IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	))))))))))	**Redacted - Public Verfsion** C.A. No. 23-975-RGA-SRF [redacted] -

DEFENDANT LIQUIDIA TECHNOLOGIES, INC'S APPENDIX OF EXHIBITS IN SUPPORT OF ITS ANSWERING BRIEF IN OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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3	Email from Sanya Sukduang dated Feb. 26, 2024 (LIQ_PH-ILD_00000024)	DA0026
4	Mar. 15, 2024 Deposition Transcript of Dr. Frederic Selck (LIQ_PH-ILD_00000597)	DA0034
5	Email from Michael Flynn dated Feb. 22, 2024 (LIQ_PH-ILD_00000031)	DA0106
6	U.S. Patent No. 11,826,327 (UTC_PH-ILD_005310)	DA0110
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8	Sept. 15, 2021 Deposition Transcript of Dr. Lewis Rubin (excerpted) (LIQ_PH-ILD_00000668)	DA0188
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20	Steven D. Nathan et al., *Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study*, 9 LANCET RESPIRATORY MED. 1266 (2021) (LIQ_PH-ILD_00000216)	DA0550
21	Agarwal M, et al., *Inhaled Treprostinil in Group-3 Pulmonary Hypertension*, J HEART LUNG TRANSPLANT 2015; 34: Suppl:S343. Abstract (UTC_PH-ILD_009828)	DA0561
22	Rajeev Saggar et al., *Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis*, 69 THORAX 123 (2014) (LIQ_PH-ILD_00000226)	DA0563
23	Aaron Waxman et al., *Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease*, 384 N. Eng. J. Med. 325-34 (2021) (UTC_PH-ILD_010790)	DA0585

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31	Savan Patel et al., *Robustness of Yutrepia™, a Dry-Powder Inhaled Formulation of Treprostinil, in Patient Misuse Scenarios*, CHEST (Oct. 25, 2022), available at https://investors.liquidia.com/static-files/0f869d92-5ad1-4db6-b75d-45149818ec2a (LIQ_PH-ILD_00000535)	DA0934
32	Liquidia Corporation Corporate Overview (June 20, 2022), available at https://www.liquidia.com/static-files/be6ab802-4090-4627-ade0-6623b6c09f24 (LIQ_PH-ILD_00000536)	DA0936
33	United Therapeutics Corporation Reports Fourth Quarter and Full Year 2023 Financial Results (Feb. 21, 2024), available at https://ir.unither.com/press-releases/2024/02-21-2024-110027752 (LIQ_PH-ILD_00000564)	DA0965
34	K. Parikh., et al., *Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension*, J. CARDIOVASC PHARMACOL. 67(4); 322–25 (2016) (UTC_PH-ILD_010599)	DA0979
35	M. Faria-Urbina, et al., Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease, *Lung* 196:139–46 (2018) (UTC_PH-ILD_009936)	DA0992
36	United Therapeutics Corporation Announces $1 Billion Accelerated Share Repurchase Program (Mar. 25, 2024), available at https://ir.unither.com/press-releases/2024/03-25-2024-110046740 (LIQ_PH-ILD_00000577)	DA1001

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37	*Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, U.S. Patent No. 10,716,793, Jan. 8, 2022 Deposition Transcript of Dr. Aaron Waxman (Ex. 1108) (LIQ_PH-ILD_00000579)	DA1004
38	Physician endorsed letter advocating for the availability of Yutrepia™ to meet the need of PH-ILD patients (LIQ_PH-ILD_00000596)	DA1022
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/s/ Nathan R. Hoeschen

Karen E. Keller (No. 4489)
Nathan R. Hoeschen (No. 6232)
Emily S. DiBenedetto (No. 6779)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
kkeller@shawkeller.com
nhoeschen@shawkeller.com
edibenedetto@shawkeller.com
Attorneys for Defendant

OF COUNSEL:
Sanya Sukduang
Phillip E. Morton
Jonathan Davies
Adam Pivovar
Brittany Cazakoff
Rachel Preston
COOLEY LLP
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004-2400
(202) 842-7800

Ivor Elrifi
COOLEY LLP
55 Hudson Yards
New York, NY 10001-2157
(212) 479-6000

Daniel Knauss
Lauren Strosnick
Kyung Taeck Minn
Sam Blankenship
COOLEY LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
(650) 843-5000

Dated: April 1, 2024

CERTIFICATE OF SERVICE

I, Nathan R. Hoeschen, hereby certify that on April 1, 2024, this document was served on the persons listed below in the manner indicated:

BY EMAIL

Jack B. Blumenfeld
Michael J. Flynn
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@morrisnichols.com
mflynn@morrisnichols.com

Douglas Carsten
Art Dykhuis
MCDERMOTT WILL & EMERY LLP
18565 Jamboree Road, Suite 250
Irvine, CA 92615
(949) 851-0633
dcarsten@mwe.com
adykhuis@mwe.com

William C. Jackson
Katherine Cheng
GOODWIN PROCTER LLP
1900 N Street NW
Washington, DC 20036
(202) 346-4000
wjackson@goodwinlaw.com
katherinecheng@goodwinlaw.com

Eric T. Romeo
GOODWIN PROCTER LLP
100 Northern Avenue
Boston, MA 02210
(617) 570-1000
eromeo@goodwinlaw.com

Adam W. Burrowbridge
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, NW
Washington, DC 20001-1531
(202) 756-8000
aburrowbridge@mwe.com

/s/ Nathan R. Hoeschen

Karen E. Keller (No. 4489)
Nathan R. Hoeschen (No. 6232)
Emily S. DiBenedetto (No. 6779)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700
kkeller@shawkeller.com
nhoeschen@shawkeller.com
edibenedetto@shawkeller.com
Attorneys for Defendant

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EXHIBIT 1

S&P Global
Market Intelligence

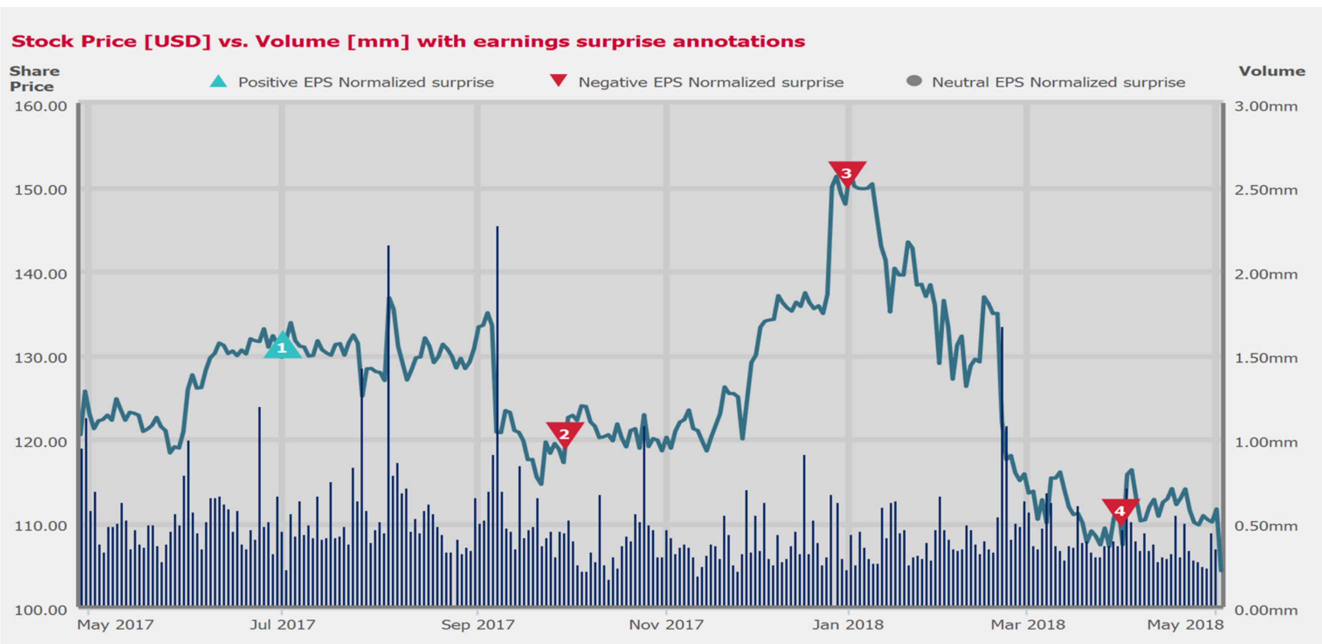
United Therapeutics Corporation
NasdaqGS:UTHR
FQ1 2018 Earnings Call Transcripts

Wednesday, May 02, 2018 1:00 PM GMT

S&P Global Market Intelligence Estimates

	-FQ1 2018-			-FQ2 2018-	-FY 2018-	-FY 2019-
	CONSENSUS	ACTUAL	SURPRISE	CONSENSUS	CONSENSUS	CONSENSUS
EPS Normalized	4.00	3.76	▼(6.00 %)	3.90	13.14	11.35
Revenue (mm)	393.96	389.20	▼(1.21 %)	379.61	1432.88	1221.76

Currency: USD
Consensus as of May-01-2018 11:15 AM GMT



- EPS NORMALIZED -

	CONSENSUS	ACTUAL	SURPRISE
FQ2 2017	3.66	4.37	▲1 19.40 %
FQ3 2017	4.80	4.69	▼2 (2.29 %)
FQ4 2017	4.58	3.89	▼3 (15.07 %)
FQ1 2018	4.00	3.76	▼4 (6.00 %)

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Call Participants

EXECUTIVES

James C. Edgemond
CFO & Treasurer

Martine A. Rothblatt
Founder, Chairman & CEO

Michael I. Benkowitz
President & COO

ANALYSTS

Geoffrey Christopher Meacham
Barclays Bank PLC, Research Division

Hartaj Singh
Oppenheimer & Co. Inc., Research Division

Terence C. Flynn
Goldman Sachs Group Inc., Research Division

Vasiliana Vireen Moussatos
Wedbush Securities Inc., Research Division

Presentation

Operator

Good morning and welcome to the United Therapeutics Corporation First Quarter 2018 Earnings Call. My name is Ashley, and I will be your conference operator today. [Operator Instructions]

I would now like to turn the conference over to James Edgemond, Chief Financial Officer of United Therapeutics.

James C. Edgemond
CFO & Treasurer

Good morning. It is my pleasure to welcome you to the United Therapeutics Corporation First Quarter 2018 Earnings Call. Accompanying me today on the call are Dr. Martine Rothblatt, our Chairman and Chief Executive Officer; and Mr. Michael Benkowitz, our President and Chief Operating Officer.

Remarks today will include forward-looking statements representing our expectations or beliefs regarding future events. These statements involve risks and uncertainties that may cause actual results to differ materially. Our latest SEC filings, including Form 10-K and 10-Q, contain additional information on these risks and uncertainties. We assume no obligation to update forward-looking statements.

Today's remarks may also include financial measures that are not prepared in accordance with U.S. Generally Accepted Accounting Principles. Reconciliations of non-GAAP financial measures to the most directly comparable GAAP financial measures can be found on our earnings release available on our website at www.unither.com.

Today's remarks may discuss the progress and results of clinical trials or other developments with respect to our products. These remarks are intended to solely educate investors and are not intended to serve as the basis for medical decision making or to suggest that the products are safe and effective for any unapproved or investigational uses. Full prescribing information for the products is available on our website.

Now I want to turn the call over to Dr. Rothblatt for an overview of the first quarter 2018 business activity of United Therapeutics.

Martine A. Rothblatt
Founder, Chairman & CEO

Thank you, James. Good morning, everyone. As James mentioned, I'm glad to also be joined on this earnings call for the first time, Mike Benkowitz, our President and Chief Operating Officer.

After my introductory remarks, we'll open up the call to any questions. And if there are questions of a financial nature, I will ask that they be answered by James, our CFO. If there are questions of a commercial nature, I'll ask that they be answered by Mike Benkowitz as our President. And if there are questions of a clinical development type of nature, then I will handle those myself.

Starting with our top line financial results. For the first quarter of 2018, our quarterly revenues totaled $389 million, an increase of 5% year-over-year. Orenitram posted a fourth consecutive quarter of greater than 20% revenue growth on a year-over-year basis. In addition, we continue to treat an increasing number of pulmonary arterial hypertension patients with our prostacyclin product franchise, which consists of Orenitram, Remodulin and Tyvaso, confirming our belief in the organic growth opportunity for these proven therapies.

The sequential drop in our total revenues from the fourth quarter of 2017 reflects consistent historical patterns as our first quarter revenues tend to be either down or virtually flat when compared to the prior year fourth quarter. This pattern reflects distributor purchases that are typically placed once a month based on current utilization trends and contractual minimum inventory requirements. As a result, quarterly

sales of Remodulin, Tyvaso and Orenitram can vary depending on the timing and magnitude of these orders and do not precisely reflect changes in underlying patient demand.

So let's now transition to our pipeline, which currently has over 20 investigational programs, including therapies for PH and other forms of pulmonary hypertension, drug delivery devices, gene therapy, oncology and technologies to ultimately create an unlimited supply of tolerable, transplantable manufactured organs for those who suffer from end-stage organ disease.

The first of our near-term and medium-term pipeline products is the Implantable System for Remodulin, or ISR. Excitement and anticipation from both physicians and patients continues to build around potential FDA approval of the ISR. This should be a game-changing technology for PH patients, and we continue to believe that thousands of patients will eventually use the ISR.

I am reminded through videos and e-mails directly from ISR clinical trial patients of the numerous ways that the ISR has impacted their lives, even for some of the most basic activities that many of us just take for granted. Activities like sleeping, showering and swimming become more straightforward for patients using the ISR. The ISR also has the potential to address complications currently associated with the use of external microinfusion pumps, including the serious risk of external catheter-related infections, like sepsis, while returning to patients the lost several hours of pump management and therapy preparation time each day to productive use.

From a regulatory perspective, the FDA approved Medtronic's PMA for the ISR in December 2017, which is 1/2 of the regulatory process. We then resubmitted our NDA for use of Remodulin in the ISR, which has been accepted as a Class II resubmission for a 6-month review. We anticipate FDA action on our NDA by July 30, 2018.

Although no FDA process is free from doubt, we remain confident that the FDA will approve the ISR in 2018. We are approaching the ISR launch with our partner, Medtronic, with precision and care to ensure that implant surgeons, refill centers, reimbursement pathways and other healthcare service organizations are all in place and properly trained and ready for commercial launch by early 2019. Our expectation that it will be ultimately used by thousands of patients is a longer-term goal as launching a surgically impacted device needs to be done carefully, thoughtfully and systematically.

Yet another next-generation drug delivery system we are advancing is RemUnity, a small, lightweight external subcutaneous pump we are developing under an exclusive agreement with DEKA Research & Development Corp. The RemUnity system uses acoustic volume-sensing technology to deliver Remodulin with a high degree of precision, representing a significant advance in microinfusion technology. In February 2018, DEKA filed RemUnity with the FDA under a 510(k) submission that was accepted for review by the FDA.

Let me now provide you an update on 4 of our 7 ongoing Phase III clinical trials.

FREEDOM-EV. FREEDOM-EV is a Phase III clinical trial using Orenitram in combination with a single ETRA or PDE-5 background therapy for PAH WHO Group I patients. This trial has a primary endpoint of time to clinical worsening. FREEDOM-EV enrolled nearly 700 patients. And we have now accumulated enough events needed to meet the required 205 adjudicated clinical worsening events that's required to unblind the study, which are expecting to do later this year.

It is also worth noting that Orenitram is the only true oral prostacyclin analog which could be dosed to therapeutic benefit. Based on patient and physician feedback, I believe that we will see continued Orenitram growth, further accelerated in the event that a possible FREEDOM-EV readout, providing the Orenitram label with a morbidity, mortality endpoint supported by good clinical trial data in use of combination therapy.

Another major and exciting event we anticipate by year end 2018 is the unblinding of our BEAT combination therapy clinical trial for PAH WHO Group I patients. This is a unique clinical trial that has never been tried in PAH before combining Tyvaso, our inhaled treprostinil therapy to treat PAH where the alveoli meet the pulmonary arterials, with Tysuberprost, and orally administered therapy to treat PAH systemically, where the blood flows from the right side of the heart into the pulmonary arteries all the way

down to the pulmonary arterials. Our data demonstrates that attacking the disease in these 2 different ways may yield better results. And similar to FREEDOM-EV, the BEAT clinical trial has a primary endpoint of time to clinical worsening.

To illustrate how we are endeavoring to create new Blue Ocean market opportunities in pulmonary hypertension WHO Group III, where we think we can have a significant and positive impact on patients with unmet medical needs, I would like to now discuss 2 additional Phase III clinical trials.

Our INCREASE trial is examining the effect of Tyvaso for WHO Group III PH associated with interstitial lung disease. Currently, this Phase III study is about 50% enrolled. There are no approved therapies for this indication. And in fact, systemic drugs like our own tablets and parenteral therapies, as well as those of our competitors, are contraindicated for this condition.

Next, I would like to move to another subset of WHO Group III PH associated with chronic obstructive pulmonary disease, or COPD, in our PERFECT Phase III clinical trial. No therapy has ever been approved by the FDA for pulmonary hypertension incident to so many of these COPD patients. And I really want to salute Dr. Waxman and his great team up at Boston who have brought this unmet medical need to our attention.

Finally, I would like to talk about UT's revenue growth strategy, particularly as we are facing increasing generic competition. As previously discussed, we expect our 2018 revenues to decrease compared to 2017 primarily due to the impact of anticipated generic competition for Adcirca beginning in mid-2018 as well as generic Remodulin, which could be launched as early as June '18. Our strategy to take advantage of the existing organic growth opportunity we have within the treated PAH patient with our existing prostacyclin product franchise including Remodulin, Tyvaso and Orenitram and to combine this with our new and improved formulations and delivery devices that I described earlier to enable us to resume revenue growth by the end of 2019.

Now I'd like to walk you through how we expect to drive this growth. First, we believe that Remodulin will continue to be a steady performer, but it will look very different from the Remodulin you see today. It will be delivered through multiple next-generation drug delivery systems intended to enhance safety, tolerability and convenience, including the ISR and RemUnity which I previously mentioned. In addition, we are developing RemoPro, a prodrug version of treprostinil expected to reduce or eliminate site pain associated with the subcutaneous Remodulin. We expect to file an IND for RemoPro later this year as we begin Phase I clinical studies.

On Monday, we also announced an agreement to acquire SteadyMed Limited. Assuming that deal closes later this year, their pipeline product, Trevyent, will sit well within UT's next generation of innovative drug-delivery systems for PAH patients.

Second, we will continue to believe in the organic growth opportunity of the treated PAH population, which we believe currently underutilizes prostacyclin therapy. Unlike other therapies on the market, UT's prostacyclin analogs can be titrated to therapeutic benefit as PAH progresses, therefore offering patients the opportunity to transition between Remodulin, Tyvaso and Orenitram as each contains the same proven active ingredient, treprostinil. This is our continuum of care advantage.

Third, we expect to grow through the introduction of new products and new indications. We currently have 6 Phase III studies in PH and 1 Phase III study in oncology. Let me itemize what these are. Two clinical trials, FREEDOM-EV and BEAT in PAH, are expected to unblinded in 2018. Three clinical trials, INCREASE, PERFECT and SOUTHPAW in PH, are currently enrolling patients and remain on track to launch commercially within the timelines currently provided in our website. These 3 clinical trials for PH are in indications which we do not have any approved therapies in place today. Three, our SAPPHIRE gene therapy study for PAH. And lastly, our DISTINCT study of dinutuximab in small cell lung cancer. These and other R&D programs are designed to provide revenue growth in the near and medium term while additional R&D programs are underway to develop technologies in organ manufacturing over the longer term.

In closing, at United Therapeutics, we are focused on the development and commercialization of innovative products to address the unmet medical needs of patients to deliver long-term revenue growth to our stakeholders. We continue to advance numerous pipeline priorities to help keep patients alive, and in effect, building bridges for them as we pursue new technologies to create an unlimited supply of tolerable, transplantable manufactured organs.

Thank you for joining us on the call today. Operator, I would like now to open the call to questions.

Question and Answer

Operator

[Operator Instructions] Our first question comes from Terence Flynn of Goldman Sachs.

Terence C. Flynn
Goldman Sachs Group Inc., Research Division

Martine, I think there was some new commentary in the Q about potential launch dynamics of the implantable pump. I think you're -- it sounds like Medtronics Limited do about 100 pumps out of the gates and then maybe making some improvements upon that. Can you give us a little bit more details about kind of the process, next steps and how to think about that ramp as we look into 2019 and beyond?

Martine A. Rothblatt
Founder, Chairman & CEO

Yes, Terence. Good to actually hear you on the phone, so that's amazing. As far as the implantable pump program, I don't -- I wouldn't get hung up on any limits or I can't give credence to the numbers that you mentioned at all. What is the situation with the Medtronic pump is that we are awaiting approval of the second half of the NDA from the FDA. And we expect that we should have -- we should hear from the FDA by the end of July. Once that happens, Medtronic and us intend to roll out these pumps to every pulmonary hypertension patient that can benefit from it. And I do believe that, that number is in the thousands, and in the high thousands. The reason for that, Terence, is that the pump allows the treatment of the disease to be all but forgettable for the patients. There's nothing they have to do to prepare their infusions. They have no open wounds or painful marks on their skin. And the drug can automatically be delivered systemically, providing them an ideal sort of PK/PD situation on treprostinil. The physicians are very, very happy with the drug. The patients are very, very happy with the drug. Now there is a fair amount of intriguing research, although nothing that has ever been approved on a label, to show that the earlier you start treating a patient with a true prostacyclin, the longer the patient is going to live. And this data has been presented at medical conferences like the American Heart, American Thoracic Society, going back to the early 2000s. The problem, Terence, is that it's been so difficult to provide a patient continuously bioavailables, in other words, 0-order delivery, true prostacyclin that patients, instead of starting on it at the very beginning of their disease, they take it at the very end. And as we all know, when 1 or 2 leaves are maybe turning brown on a plant, you could do some nutrients and get it going again. But once the plant is on its last leg, it's very hard to do things to bring it back to being a fresh, green plant again. So the remarkable thing about the Implantable System for Remodulin is that physicians could prescribe this as a front line therapy for person that has pulmonary hypertension. And instead of a patient saying, "Oh, why do I have to be burdened with an indwelling Hickman catheter?" Or "Why do I have to be burdened with transcutaneous, transdermal site pain?" They won't have to ask those questions. It will be actually easier than the Adcirca pill that they would swallow. So it will become the easiest way to treat pulmonary hypertension. And at least from the study that was used for Flolan to be approved, a very, very potent and powerful study, drug when used earlier. As you know, in the Flolan study, it was actually shown to provide a [indiscernible] benefit by starting the patients on Flolan. So we're really excited about that. I think the numbers of patients, I think I mentioned a couple of times, are going to be in the thousands. To give -- and actually, as I mentioned, I think we're probably looking at much closer to 10,000 than the number of patients that you see on parenteral drugs today which are in the low single digit thousands. And in fact, there are some physicians that we've been talking to that, if they went ahead and were to use this as front line therapy, as I've just sketched out, you would actually have something like 20,000, 30,000 patients on the Implantable System for Remodulin. As these patients live longer, that number would grow to 40,000 to 50,000 because the total prevalence of pulmonary hypertension would increase, given that the incidence is fairly constant. So this is a -- I think the word I used in my introductory remarks, this is a game-changer, Terence. And we at UT are really not hung up, we're not counting, we're not projecting what the number of patients are going to be quarter to quarter to quarter. We're committed to this program for the long haul, for the balance of the 2020s. And I personally am quite

convinced that once approved by the FDA and opened up to the market, you will see high numbers of thousands of patients on this therapy. Thanks, Terence, for the question.

Operator

Our next question comes from Geoff Meacham of Barclays.

Geoffrey Christopher Meacham
Barclays Bank PLC, Research Division

So let me ask you a question on Orenitram. When you look at the FREEDOM-EV study, it sounds like you have -- may have data by year end. What would you characterize as an incremental PH patient that could go on, assuming you have positive data? And is there a hurdle you think you have to hit in terms of time to worsening? Is it comparative to Actellion, or is it just a stat sig benefit?

Martine A. Rothblatt
Founder, Chairman & CEO

Yes, thanks, Geoff. Great question. Because that's really a kind of a commercial operations question in terms of who would be the patients that would most likely form the growing number of Orenitram patients. As you heard, we're doing quarter after quarter after quarter of strong revenue growth on that, over 20% up every time year-over-year. But all that is great tribute to the med affairs and the reimbursement. There's global supply chain management. And last but not least, the sales and marketing force that is under Mike Benkowitz. So Mike, could you answer Geoff's question?

Michael I. Benkowitz
President & COO

Sure. Thanks, Martine. Thanks for the question. Yes, I think the -- what we're seeing in the marketplace right now is the typical Orenitram patient tend to be your earlier-diagnosed patients or patients that are earlier on in their disease state because they need the time to start on therapy, titrate up. And what we have found is starting those patients earlier, when they have time to titrate up on therapy, they're able to manage the side effects better, and they just have, just generally, a better experience with the drug. And I think even without the clinical worsening label, we feel like we're getting a good share of those patients in relation to what J&J is seeing with Uptravi. I think the label -- the benefit of the clinical worsening label will put us on par with Uptravi, and I think, will allow us to capture even a greater portion of those patients because we'll now have the same clinical worsening benefit on our label in addition to being, really, a true prostacyclin. And then having the ability to put patients on that prostacyclin earlier, titrate them up, and then as Martine talked about in her comments, as the disease progresses, easily transition them over to Tyvaso or Remodulin as they continue in their disease.

Martine A. Rothblatt
Founder, Chairman & CEO

Excellent, Mike. Excellent, excellent.

Operator

Our next question comes from Hartaj Singh of Oppenheimer.

Hartaj Singh
Oppenheimer & Co. Inc., Research Division

Just -- I just want to see, Martine, if you could dig a little bit deeper into the scientific rationale going in Tyvaso in ILD and then also in COPD; and then Orenitram and the heart failure, the Phase III studies. I mean, what's the thought, the scientific sort of rationale behind, and the mechanism of action using treprostinil to go after these disorders?

Martine A. Rothblatt
Founder, Chairman & CEO

Thank you, Hartaj. Great, great question. So let's talk about the science between -- behind the INCREASE and the PERFECT studies which are the ILD and COPD studies, respectively; and the science behind the SOUTHPAW study, which is the left heart failure study. So given the limitations on the time on the call, let me, in a sense, drop to one kind of bottom line, starting with the COPD and ILD. Treprostinil, Tyvaso is not on label for patients with these indications. And as you would expect, it's not an inexpensive therapy, and payers don't just, like, blindly push the pay button on Tyvaso. Every patient is carefully assessed by payers in ensuring that it's an appropriate patient that they're obligated to pay for and not an experimental patient. Having said that, both through the effort of our medical affairs group over the years in supporting investigator-sponsored studies and through the kindness and generosity of certain payers around the country who have gone ahead and upon the initiative of their physicians, were able to enable some WHO Group III patients to benefit, there were unmistakable signals the some of the leading physicians in this field. I called out one of them on the call, Dr. Waxman, but there are many others, who said to UT, "This drug works." In fact, they believe that this drug works even better in that indication than in the Group I indication in terms of, at least, the exercise ability that they saw in their patients, discounting any placebo effects that might be involved. So with that kind of data, some of which has been presented in posters and maybe even publications -- I don't know, but I've definitely seen posters, we went ahead and then had the statistics to power of the study for statistical significance, the one in the ILD population and the other in the COPD population, which are 2 distinct populations. I believe that when you take a look at animal models of pulmonary hypertension and even when you take a look at autopsy of pulmonary hypertensive lungs after they've -- autopsy is not the right word, sorry. Biopsied. Pulmonary hypertension lungs, after they've been ex-planted for a lung transplant, you could see that the disease has a unique, and I would say, worst-case phenotype in the pulmonary arterial immediately adjacent to the alveoli. And this is the part of the arterial that is being reached most densely by Tyvaso before it dissipates through the venous drainage and circulation. So we think that the triple properties that treprostinil and Tyvaso in particular are known for, namely the vasodilating, the de-platelet-ing, but most important of all, the cytoprotective property of prostacyclin is they will lead to stop a damaged phenotype from getting more damaged, and in fact, to mitigate against damage setting in, in an inflammation setting in the first place. This cytoprotective property for this kind of -- it's hard to imagine, but if you dive deep, deep, deep in the lungs, when you get, like, past 16, 17 branches and you're have at these 10-micron wide arterials that then wrap around the air sac or alveoli, those are the ones that spell doom for the patients with pulmonary hypertension secondary to ILD or COPD. And that's what Tyvaso directs itself to immediately. At the same time, because these patients have a great difficulty with ventilation due to these deteriorated arterials around their alveoli, if you go ahead and you just give -- you just take advantage of the anatropic properties of prostacyclin, mainly kind of making the heart pump stronger, then you get into this thing called perfusion ventilation mismatch or V/Q mismatch. And that, unfortunately, can lead to fatal events for the patient. So the strongest science here is really on the ability to help pulmonary hypertension patients who have COPD and ILD, so-called WHO Group III pulmonary hypertensions. They have some other distinctive characteristics. They're in the tens of thousands. They are not being treated for their pulmonary hypertension today. There's nothing on label for it. To be able to treat them with the only type of agent, an inhaled agent that can successfully treat them where they need the help the most and where it will not cause the devastating side effects of V/Q mismatch. Now turning over to the last part of your question, on SOUTHPAW, there are 2. Hartaj, it's gone back for -- actually for decades, that people thought treprostinil would be useful for left heart failure. And indeed, it was -- its very first trial was in congestive heart failure back when this was a molecule owned by Burroughs Wellcome. So what the problem is though is, to do a proper CHF trial, you're usually talking about thousands of patients, and it was tried just in a couple dozen patients. And it was a -- what we would call, I mean, if you wanted to map the word from cancer over to left heart failure, it was like a basket study. It was just everybody was thrown in there with no understanding of the distinctions among the patients. There has been opinions over the years, strengthened again with the same kind of evidence that I described for the PERFECT and INCREASE studies, that if you targeted just the subset of heart failure patients that had preserved ejection fraction, that the suite of properties associated with prostacyclin, I had mentioned the unique anatropic profile of this agent, would in fact be very, very helpful for these patients. And we were really blessed to be led in the area by a superb cardiologist with great experience, Dr. Mardi Gomberg. And she is the lead investigator for our SOUTHPAW study. And I think it has always been a strong property of prostacyclin to impact the heart. The problem is to do so in the way without making things worse and to do so in a

way that it addresses a particular type of heart failures that the individual has. SOUTHPAW is -- I'm sorry, Orenitram, of course, is not any kind of a cure for heart failure per se. But if part of your heart failure is accompanied by HFpEF heart failure with preserved injection fraction, then we believe the data that led us to our hypothesis with HF, is that there is a significant likelihood that we can moderate the overall heart failure rate of decline by addressing the subset that has HFpEF. And so that's the group that we'll be targeting with this agent.

I'm being told that we have time for one more question.

Operator

Our last question comes from Liana Moussatos of Wedbush.

Vasiliana Vireen Moussatos
Wedbush Securities Inc., Research Division

You mentioned that the DEKA pump has been accepted by the FDA, a 510(K). And when do you think you can get it approved? Last call, you said early 2019. Is it on track for that?

Martine A. Rothblatt
Founder, Chairman & CEO

Thanks, Hartaj -- I mean, thanks, Liana. Sorry about that. Yes. So let me, like, back up. Whatever I said in the last call, I still think is good. So I'm not changing anything from the last call. The pump is a really fascinating piece of machinery, Liana. And the more I see it in operation, the more just kind of completely blown away I am by it. It's got virtually no moving parts. In fact, actually the pump itself has no moving parts. And I think it's a kind of like a Tesla of pumps. Like a regular car has something like thousands of moving parts, and a Tesla, I think they advertised it as 20 or 25 moving parts. So of course, regular infusion pumps don't have thousands of parts, but they got a lot of parts. And just ask the poor patients who have to put all the pieces together every day or 2 on their table, takes up like half a dining room table. But with the DEKA unity pump, there are no moving parts due to the inventive geniuses of those folks. So this is going to be a super cool device. Of course, we will ship it to the patient with the drug already supplied to eliminate the need for the patients to have any errors in the process of drug fill. And also to buy back for the patient a very, very valuable hours of their time, which is otherwise spent on refilling these pumps. We also have the rights, Liana, to use this pump technology for additional drugs for other [orphan] diseases. And we have now begun a program in Parkinson's disease based on using the same pump technology, the same pumps, actually. So it's really a super exciting program. Of course, and as I mentioned in my introductory remarks, nobody can predict the FDA exactly. And the FDA is going to make the decision. And I've been right sometimes, been wrong sometimes, I'm not going to -- like, I don't make any more bets on the these things. But I will say this, that you were looking at a sponsor, DEKA, that has successfully obtained FDA approvals for every product that they have taken through the FDA, including some truly revolutionary products, such as bioelectronic prosthetic arms, Class III medical devices. I mean, very, very challenging approval. Dialysis machines for Baxter, multiple generations of those. So this is an organization that definitely has, to my knowledge, 100% success record at the FDA. And I'm confident that they will take this through. And wow, these are not -- United Therapeutics also has 100% success record at the FDA, because Remodulin, Tyvaso, Orenitram, Unituxin. So I believe, between the 2 of us, I could not be more confident, Liana, that we will be able to successfully launch this RemUnity pump. Exactly which month, who knows? It's up to the FDA. But I stand by everything I've said before.

Thanks, Liana. And operator, if you could please do your wrap up comments.

Operator
Thank you for participating in today's United Therapeutics Corporation Conference Call. A rebroadcast will be available for replay for 1 week by dialing 1 (855) 859-2056, with international callers dialing 1 (404) 537-3406 and using access code 5778455.

EXHIBIT 2

REFINITIV STREETEVENTS

EDITED TRANSCRIPT

UTHR.OQ - Q4 2022 United Therapeutics Corp Earnings Call

EVENT DATE/TIME: FEBRUARY 22, 2023 / 2:00PM GMT

OVERVIEW:

Co. reported 4Q22 results.

REFINITIV

CORPORATE PARTICIPANTS

Dewey Steadman *United Therapeutics Corporation - Head of IR*

James C. Edgemond *United Therapeutics Corporation - CFO & Treasurer*

Leigh Peterson

Martine A. Rothblatt *United Therapeutics Corporation - Founder, Chairman & CEO*

Michael I. Benkowitz *United Therapeutics Corporation - President & COO*

CONFERENCE CALL PARTICIPANTS

Andreas Argyrides *Wedbush Securities Inc., Research Division - Analyst*

Ashwani Verma *UBS Investment Bank, Research Division - Director of Americas Equity Research & US Specialty Pharma Analyst*

Hartaj Singh *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Jessica Macomber Fye *JPMorgan Chase & Co, Research Division - Analyst*

Joseph John-Charles Thome *Cowen and Company, LLC, Research Division - MD & Senior Research Analyst*

Justin Hovsep Simonian Phillips *Morgan Stanley, Research Division - Research Associate*

PRESENTATION

Operator

Good morning and welcome to the United Therapeutics Corporation Fourth Quarter and Full Year 2022 Earnings Webcast. My name is Devin, and I will be your conference operator today. (Operator Instructions) I will now turn the webcast over to Dewey Steadman, Head of Investor Relations at United Therapeutics.

Dewey Steadman - *United Therapeutics Corporation - Head of IR*

Thanks, Devin, and good morning. It is my pleasure to welcome you to the United Therapeutics Corporation Fourth Quarter and Full Year 2022 Earnings Webcast. Accompanying on today's webcast are Dr. Martine Rothblatt, our Chairperson and Chief Executive Officer; Michael Benkowitz, our President and Chief Operating Officer; James Edgemond, our Chief Financial Officer and Treasurer; Pat Poisson, our Executive Vice President of Technical Operations; and Dr. Leigh Peterson, our Senior Vice President of Product Development.

Remarks today will include forward-looking statements representing our expectations or beliefs regarding future events. These statements involve risks and uncertainties that may cause actual results to differ materially. Our latest SEC filings, including Forms 10-K and 10-Q, contain additional information on these risks and uncertainties. We assume no obligation to update these forward-looking statements.

Today's remarks may also discuss the progress and results of clinical trials or other developments with respect to our products. These remarks are intended solely to educate investors and are not intended to service the basis for medical decision-making or to suggest that any products are safe and effective for any unapproved or investigational use. Full prescribing information for the products are available on our website.

And United Therapeutics executives will participate in 3 investor conferences in March. First, Michael Benkowitz will participate in a fireside chat at the Cowen Healthcare Conference on Tuesday, March 7. Dr. Martine Rothblatt will participate in a fireside chat at the Oppenheimer Healthcare Conference on Monday, March 13, and our Chief Medical Officer, Gil Golden will participate in the JPMorgan Napa Valley Biotech Forum on Tuesday, March 21.

Now I will turn the call over to Dr. Rothblatt for an overview of the fourth quarter and full year 2022 financial results and business activities of United Therapeutics. Dr. Rothblatt?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, Dewey, and good morning, everyone. I feel very excited to lead this call because we have so much positive news to report about 2022.

In fact, I -- reflecting back on the past few years, this is actually the best year United Therapeutics has ever had. And it augurs even more, I think, positively to what we're going to see coming up in 2023, 2024 and 2025.

Let me hit a few highlights. First, 2022 was our highest revenue year ever. Second, 2022 was our most profitable year ever. Third, 2022 was our highest operational cash flow year ever. And fourth, we ended 2022 with more patients on our treprostinil medicines than ever before.

I think you have to agree with me that these are fantastic results. And now I'd like to give a few indications of why I think that as great as these results are, they are not laurels for us to rest upon but instead a launching pad for yet greater results in 2023, 2024 and 2025.

In fact, the patient uptake of our new Tyvaso DPI medicine has been so rapid that we can project a doubling of our revenues by 2025. This doubling of revenues is helped by the unique nature of each of our medicines including Tyvaso DPI. For example, Tyvaso DPI is the only inhaled treprostinil product that enables deep lung penetration via high-resistance low-flow device.

Another example, our Remodulin product is the only parenteral prostacyclin delivered by the small, easy, super accurate Remunity device. The differentiated aspects of Remodulin has allowed us revenues to remain steady at about $0.5 billion a year through the past 3 years running.

Our Orenitram product is also very unique because it is the only titratable oral prostacyclin product. We currently expect it's 1/3 of $1 billion a year revenue to continue growing as physicians become aware of the results of our recently released EXPEDITE study. That study showed Remodulin patients can be switched directly to Orenitram. And Orenitram will soon be joined by new products from our pipeline.

In the field of pulmonary arterial hypertension, we expect to complete our Phase III trials of ralinepag by 2025. That will enable the first once-daily dosing of a prostacyclin pill in the pulmonary hypertension field.

In the field of pulmonary fibrosis, we expect to complete our Phase III trials of Tyvaso by 2025 as well. That will, we hope, create the first disease-modifying treatment for pulmonary fibrosis, a true landmark in the field.

And in the area of transplantation we hope to commence clinical trials of manufactured organs within the next few years. That would be a major contribution to ending so many deaths on the organ transplant list and unfortunately, even more deaths from end-stage organ disease off the transplant list.

In summary, our business, our patient count, our pipeline is growing longer and faster than ever before. 2022 marked the continuation of that growth factor into 2023. We have achieved a very nice balance of growth and strength. We intend to continue building on this platform in the years to come.

To provide now some additional, very median I think, extremely exciting details of how we are continuing to build on this platform, I'd like to introduce our President and Chief Operating Officer, Michael Benkowitz. Mike?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Thanks, Martine, and good morning, everyone. From a commercial standpoint, as Martine said, 2022 was a phenomenal year for us. We're extremely pleased with the progress of the Tyvaso DPI launch as referrals starts and active patients for both Tyvaso and Tyvaso DPI are among the best that we've seen to date.

We were also very excited to achieve our goal of doubling the number of Tyvaso patients following the PH-ILD approval in early 2021. This was a goal that Unitarians across the organization rallied around and supported. So we're really proud and appreciative of everyone's hard work over the last couple of years to help us reach this milestone.

Importantly, reaching this goal reinforces to us the impact that Tyvaso and Tyvaso DPI are having not only in helping patients with PH-ILD treat this serious progressive disease for which there are no other available options, but also the impact Tyvaso DPI will have in PAH. With the simple convenience of a small inhaler that fits in the palm of the patient's hand and an elegant ease of use following the simple mantra of open, load, inhale. We believe Tyvaso DPI will meaningfully expand the use of inhaled treprostinil in both indications.

The Tyvaso DPI inhaler device developed by our partner, MannKind, is able to efficiently deliver treprostinil deep into the lung and one breadth per cartridge using less active ingredient to the nebulizer reference. The convenience and efficacy of our DPI device, coupled with Tyvaso's known tolerability profile has us well positioned to expand our reach in PH-ILD and to move the use of treprostinil therapies like Tyvaso DPI and PAH even earlier than IP receptor agonist like selexipag.

We're seeing this play out with our prescribers as evidenced by several positive trends. Since the PH-ILD launch, we've increased the total number of Tyvaso prescribers by about 70%, an increase by almost 60%, the number of prescribers with 3 or more patients in their practice.

This last point is an intra marker we look at to gauge product support. We have found that once a physician has at least 3 patients on one of our products, they tend to become what we call supporters and start using the product much more frequently and regularly.

We're also making headway with traditionally loyal selexipag prescribers. Of the top 100 selexipag prescribers, 70% have now written Tyvaso DPI and 50% of those have written 5 or more prescriptions. From a revenue standpoint, we're very pleased with how the quarter and the year wrapped up for Tyvaso, but there are a few key points I want to highlight.

First and most relevant to the fourth quarter of 2022 is that we're still in a launch mode for Tyvaso DPI and even for the PH-ILD indication for that matter. As such, our specialty pharmacy distributors are still rightsizing product orders based on estimated underlying patient demand, both in total and between Tyvaso nebulized and Tyvaso DPI. Therefore, our distributors are placing orders more frequently than their once or twice a month historical cadence. And these new ordering patterns did impact the timing and size of product orders and thus our product revenues during the quarter.

Second, we're also building Tyvaso DPI inventory as we're launching a product. So our distributors are not yet able to order a sufficient product to reach contractual inventory levels per their usual practice. We expect over the next several quarters, these 2 factors will normalize, and our specialty pharmacy distributors will shift back to a more historical type cadence of product orders. For these reasons and the usual historical seasonality to our business that we have discussed on prior calls, we think annual revenue trends are a better lens through which to view and evaluate our business.

The last thing I want to touch on with Tyvaso is our patient assistance program or PAP. Patient utilization of our program -- of our PAP program for Tyvaso DPI which is covered under Medicare Part D and has high patient co-pays, has been higher than anticipated, including by many PH-ILD patients who were on the nebulizer and nPAP last year and has since transitioned to DPI.

We anticipate that this will be a short-term phenomenon and that many of these patients will be covered under their Medicare Part D plan starting in 2024 and continuing into 2025, once changes to the Part D provisions of the Inflation Reduction Act begin to go into effect.

Turning to Orenitram. We see continued momentum for Orenitram as we ended the fourth quarter with the highest number of patients on therapy since its launch. We're also excited about the recent top line EXPEDITE data we press released in October of last year that demonstrated that prostacyclin induction with Remodulin can lead to double the average Orenitram dose when patients shift to oral therapy compared to patients who do not have a Remodulin induction.

Following up on this top line data, we plan to present additional details on EXPEDITE at scientific meetings this year, along with a peer-reviewed manuscript detailing the study in the second quarter.

And finally, we continue to be pleased with the performance of Remodulin in the U.S. as the fourth quarter was one of our highest referral quarters ever. The Remunity pump for Remodulin is gaining momentum with approximately 1/3 of subcutaneous patients now on Remunity especially as Remunity is the only subcu pump widely available for any patients to treprostinil therapy.

So to wrap up, after reaching our goal of doubling the number of Tyvaso patients, we're confident in our ability to double our annual revenue run rate for approximately $2 billion today to $4 billion by the end of 2025. We expect continued Tyvaso and Tyvaso DPI uptake in both PAH and PH-ILD to drive most of our near-term revenue growth, supplemented by Orenitram growth through the expedite protocol and other research and supported by continued Remodulin resilience. With that, I'll turn the call back over to Martine.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Michael, thank you so much for providing that wealth of detailed information supporting this great growth vector we have going here from 2022 into 2023, '24, '25.

Operator, feel free to open up the lines to any questions now.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Jessica Fye with JPMorgan.

Jessica Macomber Fye - *JPMorgan Chase & Co, Research Division - Analyst*

I have 2, if that's okay. First, can you provide some of the assumptions, specifically around Tyvaso and Tyvaso DPI to help underpin your target to roughly double your revenue run rate for the overall company by the end of 2025.

And then second, just following up on Michael's comments in prepared remarks, I was hoping if you could elaborate a little bit more on that comment about the utilization of the PAP program for DPI being higher than anticipated among PH-ILD patients who transitioned to DPI. Is that to say that because of the higher out-of-pocket in Part D in the short term that they're receiving free drug? And how should we reconcile that with, I think, what was anticipated to be a bit of a tailwind in 2023 from PAP patients transitioning on to reimbursed product this year?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Yes. Thank you, Jess, and good morning. Good to hear your voice this morning. Generally, we try to like limit to one question for questioner because there are so many people in queue. But because your 2 questions are in a sense kind of like a tag team question, one way close into the next, Mike, I'll kind of ask if you can handle both questions.

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Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So I think, Jess, your first question around the assumption, the underlying assumptions for our confidence in the growth of Tyvaso in both PAH and PH-ILD is, in some ways, it's a little bit of a math -- kind of a math exercise, but also just I think -- I think just the excitement and enthusiasm we're seeing around DPI.

So if you think about in the PAH or the WHO Group 1 market, there's about, I mean, roughly 50,000 patients in the U.S. diagnosed with PAH, still and shockingly and sadly, it's probably only about, I would say, about 30% to 35% of those patients are on a prostacyclin. And there's a lot of reasons for that, and a lot of it comes down to the fact that the delivery mechanisms for prostacyclin are -- they're not terribly convenient. But I think that is changing on Tyvaso DPI. So we feel very confident that we will be able to -- with the convenience of the DPI inhaler to be able to expand the use of prostacyclins in the PAH market meaningfully.

So I think we feel like even though it's a crowded market, even though Tyvaso has been out there, we still think that there's a lot of opportunity within the WHO Group 1 market to grow the use of prostacyclin and particularly Tyvaso.

And then a similar story, but maybe a little bit easier on the PH-ILD side because there, you have a market that's conservatively 30,000 patients with no other approved therapy. And so we've roughly tapped into about 10% of that over the last couple of years, and we think we have another other 90% available to us. So we still feel like we have a lot of runway there to grow with Tyvaso. And again, I think just with the convenience of DPI, it's going to get easier for doctors to prescribe that drug for those patients that have PH-ILD.

And then shifting to your second point on the PAP. So yes, so the issue is that we had patients in PH-ILD, patients on Medicare and our PAP program for 2021, 2022, expected a lot of those to roll over starting in 2023. And a lot of those have started to roll over in 2023. It's not as high as -- the number that are rolled over, it's not as high as we expected for a couple of reasons.

One is I think at the end of the third quarter, I think we reported that there were about 700-ish patients in the PAP program. So some of those discontinued which we expected. Some of those even after becoming -- even with the CMS coverage, still qualified for PAP. And so they stayed in PAP. And then as I said in my prepared remarks, we did have a number of patients that transition to DPI between the end of the third quarter and the beginning of the first quarter. And so with the higher co-pays and Part D, they were then eligible to remain in PAP.

So I think we still had about half, slightly more than half of those patients convert over. I think they're still -- they're kind of working through the system, but it's a little bit less than we were expecting, I think, when we had the call in the third quarter.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Those are great answers. Jess, one just additional shade of color I could add on top of Mike's remarks with regard to your question as to what kind of parameters can I provide to provide greater assurance about the doubling of revenues by the end of '25 is the uptake of Tyvaso DPI has been dramatic. And as Mike mentioned, he provided some metrics, for example, the very high number of selexipag prescribers who have not previously prescribed on Tyvaso now prescribing Tyvaso DPI.

So when we achieve the doubling of our patients on Tyvaso over a period of just 18 months, I can't really overemphasize what an important metric that is. Just to give you kind of a sense, Tyvaso was approved 10 years ago. So it took like 10 years to get up to a certain level of patient penetration for this drug and then in under 2 years, it doubles. I mean that's -- it's an unmistakable sign in addition to the steps that Mike shared with you that this product is going to penetrate very, very rapidly.

Now while one might think that in an area such as PH Group III, which has been penetrated by no pulmonary hypertension medicines like, oh, these are all just like people dying of thirst and just going to just slap up this new medicine right away, the reality in a disease like pulmonary hypertension is that it just doesn't happen like that. Instead, it's a very kind of blocking and tackling exercise of physician by physician, center by center working through all of the rigorous of talking to the right payers and getting the payers to understand the right procedures and going through all the procedures and the pre-approval, diagnoses, requirements, the catheterizations and all of these things.

So while we did create like special teams focused on PH Group III before we launched into that indication, in the field of pulmonary hypertension, one year of kind of preparation is sort of like nothing compared to how much activity is needed to build a bulk of patients. So now that 1 year is more than 2 years behind us, we've now had a year of actual practice, okay, you can actually put these patients on medicines.

As Mike referred to, the payer aspects, especially with regard to Medicare, we're just very, very recently resolved favorably in our direction. And so the -- it's just you have to like first have not just 1 year and not just like there wasn't like a waiting bolus of patients in Group III just waiting for a launch, you have to like develop this market and really kind of till the soil for a number of years. We've now done that, and we're experienced in those clinics and it's this reason why we think out of those 30,000 PH Group III patients. Fortunately, none of them have been touched by pulmonary hypertension treatment that we can rapidly grow our numbers of patients at the same rate that we've been growing them for the past year with this doubling of the number of patients on Tyvaso and thereby reach a number of total treprostinil patients, something that would be in the 20,000 that would correlate when you multiply that times the reimbursement per patient to the $4 billion per year.

And of course, it's important. In addition to this, not to be losing revenue from Remodulin or Orenitram. But not only are we not losing revenue, we're solidifying our hold on the Remodulin revenues as Mike referred to the very rapid penetration that the Remunity pump has made and we're growing our revenues in Remodulin -- in Orenitram as a result of the EXPEDITE study that Mike described. So we feel that doubling revenues in 3 years is really a very doable too.

Operator, next question, please?

Operator

Our next question comes from Terence Flynn with Morgan Stanley.

Justin Hovsep Simonian Phillips - *Morgan Stanley, Research Division - Research Associate*

This is Justin Phillips on for Terence. Just one question for me. I was wondering if you could provide any details today on the Tyvaso trends for January and February.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Sure. Mike, would you like to take that?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. I'm not going to get into too much detail in terms of previewing the quarter. I mean, I think what I can tell you is and really I have got about a month of data behind us, but I can tell you that the trends in terms of referrals, that's what we call prescriptions for Tyvaso in January are very strong, had like a record level for January.

So -- and at least what I'm seeing through kind of there's a lag on the February data, but February is continuing that. So again, I think we're really pleased, just to echo what Martine said, I think we're really pleased with the uptake of generally and specifically with DPI.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, Mike. That's so nice to hear. Record January referrals after a record year, fantastic. Next question, please.

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Operator

Our next question comes from Hartaj Singh with Oppenheimer & Company.

Hartaj Singh - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Just a quick question on a slightly different topic with your plan to potentially double revenues by 2025, you still got the Tyvaso IPF Phase III trial reading out around then which is positive. Martine sense another nice little runway there. Could you maybe just go over -- remind us again if Gil is on the call, the data behind that, your certainty around that project? And then just some basic sizing of the market.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Sure, Dr. Singh, so happy to hear your voice this morning, and thank you for asking a science question. We love those questions best of all. We have on our call, Dr. Leigh Peterson, and she is our Chief Scientist for the program, and she's also running the TETON clinical trials. People often wonder why they are named TETON, and it's because Dr. Peterson is from Wyoming. So it makes perfect sense. And Leigh, if you could provide Hartaj with some of the scientific reasons why we feel very confident that the Phase III trials of Tyvaso in IPF are rightly sized and that the endpoints are rightly chosen.

Leigh Peterson

Yes, sure. Thank you for the question. As you know from the results of our INCREASE study, we had an exploratory endpoint, which was forced vital capacity. And that was really -- for the PH-ILD population, it was really a safety assessment in the study but it turned out, we actually saw an improvement of that endpoint in patients on Tyvaso and so -- relative to placebo.

And so between the results of this study, increase in PH-ILD patients as well as quite a few -- quite a bit of evidence in the literature of in vitro in nonclinical studies that Tyvaso or treprostinil does have an impact on fibrosis.

It's very reasonable that we would be able to have a positive impact in an IPF population. And so using the statistics and the treatment effect that we saw, an increase in specifically IPF patients, we were able to do sample size calculations in order to predict that we would have a successful study with a sufficient p-value to get approval. And we're actually doing 2 studies, one TETON 1 study in the U.S. and Canada as well as TETON 2, which is outside of U.S. and Canada in order to -- in each of those studies, about 400 patients -- almost 400 patients, and enrollment is going well as expected.

And as Martine -- that we expect to read out in around the 2025 time frame of both of those studies. They both have an FVC endpoint again, same as what we saw, a positive sense in INCREASE. And we have a year-long follow-up period. We've also had some published results of the INCREASE. You might remember that the randomized part of the study an INCREASE was 16 weeks, but we continue to follow patients -- those patients in a long-term open-label extension study. And so we've been collecting long-term FVC data as well, which looks promising and also gives us confidence that the TETON studies will be successful, but to be determined in 2025 time frame.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Well, thank you so much, Leigh. And I just want to and toot your horn just for a moment to the hundreds of people on the call that there was similar skepticism as to whether or not Tyvaso could work in Group III patients and you proved that it could. And I believe your results were published in the New England Journal of Medicine. So congratulations again. Next caller, please.

REFINITIV

Leigh Peterson

Thank you. Yes, they were.

Operator

Our next question comes from Ash Verma with UBS.

Ashwani Verma - *UBS Investment Bank, Research Division - Director of Americas Equity Research & US Specialty Pharma Analyst*

I have one. So for Tyvaso, was there any inventory buildup in 3Q that bind you down mostly in 4Q or do you think inventory is still at an elevated level during 4Q? I think you mentioned that specialty distributors are still rightsizing the orders.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, Ash. Thank you for that question. Fortunately, we have our Chief Financial Officer, on the phone, James Edgemond. And James, if you could perhaps help Ash with the inventory question.

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Yes. Thank you, Martine. Thank you for your question. I think there's kind of 2 ways to answer. One is Michael addressed and talked about the Tyvaso and Tyvaso DPI ordering patterns in his prepared remarks. And I think if you look at B as part of the answer, the other products there was no unusual ordering or inventory activity and our specialty pharmaceutical distributors were in line with their contractual requirements on inventory. So hopefully, that provides you insight in terms of your question this morning. So thank you, and back to you, Martine.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, James. Operator, next question please.

Operator

Our next question comes from Joseph Thome with Cowen and Company.

Joseph John-Charles Thome - *Cowen and Company, LLC, Research Division - MD & Senior Research Analyst*

We're going to be seeing the full mark of sotatercept Phase III data at ACC in about 11 days. And I was just curious how you see a potential future sotatercept launch impacting the PAH market broadly and maybe how this is reflected in that 2025 revenue run rate guidance that you announced.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Yes. Thanks for the question. So it's really like super speculative to provide any kind of a meaningful answer to the question because we don't know what the regulatory time frame is going to be for sotatercept. So it's all but impossible to give you any kind of accurate sense.

I will say that our revenue forecast is agnostic with regard to whether or not sotatercept is approved or not. In other words, we will remain confident about achieving the doubling of our revenues by 2025 without regard to its launch. There -- it's a very large and diversely treated patient population. Changes in treatment patterns are relatively slow and cautious especially other than frontline treatments such as like ETRAs or PD5s. So I'd be very,

very skeptical that you would see an impact of sotatercept on United Therapeutics revenue profile or product uptake across the board, whether it's Remodulin, Tyvaso, Tyvaso DPI or Orenitram.

More broadly, the experience has been that when new agents have been introduced into the market, it has grown the market for all of the existing patients. It's kind of like a market growth thing. You saw this with, for example, back in the day when we launched Remodulin and J&J's precursor Actelion launched bosentan, the treprostinil revenues did not shrink. In fact, they grew and then later on, when PD5s were introduced, the market for ETRAs, and treprostinil did not shrink. In fact, it grew, it grew quite a bit. And this has been just a continuous process, and it harkens back to the landmark number that you should keep in your mind that Michael Benkowitz mentioned in his remarks was 50,000, that's 5-0 thousand. That's the number of patients diagnosed with pulmonary hypertension. And all of these drugs have just like scratched the surface of being able to really treat the patients and get them back to a New York Heart Association Functional Class I or even Functional Class II level.

So there is so much robust room for growth and improvement in pulmonary hypertension. We at United Therapeutics, welcome any new agent that can help the health of the pulmonary hypertension patient population. And by the way, all that is with respect to WHO Group I pulmonary hypertension. So everything I just said, then you've got this other huge pool that Dr. Peterson opened up with her New England Journal article, WHO Group III, 30,000 patients, that's 3-0 thousand, of which the only approved treatment right now is our Tyvaso drug.

And I think sotatercept, I would love to see another good drug to help people with pulmonary hypertension. I don't think it's going to have any effect on our revenue growth.

Next question, operator, and we'll have to cut it after that due to coming to the end of time.

Operator

Our final question comes from Andreas Argyrides with Wedbush Securities.

Andreas Argyrides - *Wedbush Securities Inc., Research Division - Analyst*

Congrats on a great year. Just a quick one here on Tyvaso DPI. Are you still seeing more rapid up taking new patients versus transition? And what is the split between new and transition patients?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

A very good question. Mike, can you give us our final answer on the call?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Yes. So it's -- I think it's -- I have to go back to look, I haven't look at it in a couple of weeks, but I think it's still weighted towards new patients in terms of DPI. I mean the transitions are coming. It's just as I think I said on the last call, I think what physicians are doing is they're waiting until patients come in for the regular checkup. So they're kind of coming -- they are coming in at a healthy clip, healthier than what we were seeing and I think that will continue through the course of the year.

And so I fully expect at the end of the year, those patients that want to transition to DPI will transition to DPI. So it's certainly a kind of a point of emphasis for our sales team. And certainly, as I said -- certainly, I think the physicians are aware of it and as those patients come in and they decide that the patient is eligible to transition, they'll move them over.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, Mike. Well, to wrap up the call, we are tremendously excited about 2022. This is the year that we hit our $2 billion revenue run rate that has been our goal for really much of the past several years. And we are even more jazzed and more pumped by the fact that the $2 billion level, makes it very clear to us that $4 billion is achievable with all of the products that we are currently marketing and explaining to physicians, the scientific and medical benefits of.

And then beyond that, as Hartaj indicated in his question, we have a whole another slew of type -- of products coming out of our Phase III pipeline, particularly a whole new disease indication, pulmonary fibrosis and then on top of that, a best-in-class treatment for pulmonary hypertension, which would be Ralinepag. So 2022 was amazing, a huge kudos to everybody on the team for achieving it. 2023 is looking even better. And with that, operator, you can close out the call.

Operator

Thank you for participating in today's United Therapeutics Corporation Earnings Webcast. A rebroadcast of this webcast will be available for one week by visiting the Events and Presentations section of the United Therapeutics Investor Relations website at ir.unither.com. Have a good day.

EXHIBIT 3

From: Sukduang, Sanya
Sent: Monday, February 26, 2024 6:05 PM
To: Jackson, William C; Flynn, Michael J.
Cc: Davies, Jonathan; kkeller@shawkeller.com; Nate Hoeschen; Dcarsten@mwe.com; Cheng, Katherine; Adykhuis@mwe.com; aburrowbridge@mwe.com; Lobel, Louis; Romeo, Eric; Mhkim@mwe.com; z/Liquidia v UTC 308970-201
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

William,

We agree a TRO is a waste of time, resources and not well supported. This is an issue completely of UTC's own making. UTC knew from the date of FDA approval of PH-ILD that its regulatory exclusivity would expire at the end of March 2024. UTC filed suit in September 2023 asserting the 793 patent based on Liquidia's addition of PH-ILD and knew Liquidia intended to launch upon FDA approval. Yet, UTC did not file a PI at that time. UTC amended its complaint on November 30, 2023 to add the '327 patent, knowing Liquidia would launch and knowing the date of expiry of regulatory exclusivity—no PI was filed. On December 6, 2023, upon a direct request from you, Liquidia expressly and unequivocally informed UTC that it will launch upon final FDA approval. UTC did not file a PI then. Thus, the immediacy and harm UTC alleges is a fallacy and nonetheless, caused by UTC. These facts are not in dispute.

Liquidia will not agree to delay launching until resolution of UTC's PI motion.

Thanks
Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Monday, February 26, 2024 5:02 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; Dcarsten@mwe.com; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Adykhuis@mwe.com; aburrowbridge@mwe.com; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

[External]

Sanya:

It has occurred to us that the briefing schedule that you requested means that UTC's regulatory exclusivity on ILD will expire before the briefing on the PI is complete. It is possible that the FDA may act in the interim. Will Liquidia agree not to launch before Judge Andrews rules on the preliminary injunction motion? If not, we will be forced to file a request for a temporary restraining order, which we think is a waste of time and resources.

Let us know.

William C Jackson

GOODWIN
Goodwin Procter LLP

1900 N Street, NW
Washington, DC 20036
o +1 202 346 4216
m +1 202 270 6622
f +1 202 478 0819
WJackson@goodwinlaw.com

From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Monday, February 26, 2024 9:11 AM
To: Jackson, William C <WJackson@goodwinlaw.com>; Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; Dcarsten@mwe.com; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Adykhuis@mwe.com; aburrowbridge@mwe.com; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

EXTERNAL
William,

We disagree with many of UTC's positions below, but the facts concerning UTC's prior notice of Liquidia's intent to launch have been confirmed in your email below. We see no need for a further meet and confer.

Thanks
Sanya

From: Jackson, William C <WJackson@goodwinlaw.com>
Sent: Saturday, February 24, 2024 3:54 PM
To: Sukduang, Sanya <ssukduang@cooley.com>; Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; Dcarsten@mwe.com; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Adykhuis@mwe.com; aburrowbridge@mwe.com; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

[External]

Sanya:

As I am sure you expected, there are a number of statements and characterizations in your email below with which we disagree. For example:

1. **Question 1**: Liquidia currently is enjoined from launching based on the judgment from the prior D. Del. case. But Liquidia has a pending Rule 60 motion for relief from that judgment. The Court could rule on that motion at any time. Should that motion be granted, there would be no impediment to Liquidia launching its LIQ861 product. Should the Court grant the motion and Liquidia launch its product for ILD, UTC would be irreparably harmed. **UTC proposed that, in order to avoid having to brief a preliminary injunction now, the parties agree that, if the Court were to grant the pending Rule 60 motion in the prior case, UTC would have 5 days to file a preliminary injunction motion and Liquidia would not launch its product for the ILD indication**

during the pendency of those preliminary injunction proceedings. Such an agreement would obviate the need for a preliminary injunction motion now (and potentially at all). Liquidia has now rejected that proposal.

2. **Question 2**: The APA action against the FDA asserts that the FDA violated its own "Bundling Rule" and allowed Liquidia to seek to add the ILD indication as an amendment rather than a separate NDA. Those proceedings, alleging a violation of the Administrative Procedures Act, are entirely distinct from these proceedings in which UTC alleges that Liquidia is infringing its '327 patent. Nor is Liquidia even a party to those proceedings.
3. **Questions 3-4**: The parties did meet and confer in December about entirely different issues in this case. During that conversation, the possibility of a preliminary injunction was referenced. But I believe the focus of the meet and confer in December was the schedule for Liquidia answering or otherwise responding to the Amended Complaint that UTC had filed.
4. **Question 5**: As I indicated, in the NC case UTC has consistently sought to accommodate both parties' reasonable scheduling requests. By contrast, after providing an expert report in the NC case, Liquidia stated that its expert was available for deposition on a single day in the entire expert discovery period, including weekends, and refused to agree to extend the expert discovery period to accommodate the schedules of those involved. It was for that reason that we were forced to seek the NC court's assistance. We are corresponding with you and NC counsel with respect to the proposal to adjust the NC expert deposition calendar.
5. **Questions 6-8**: We agree with your summaries below and look forward to hearing from you with respect to the deposition dates for Dr. Nathan and Mr. Selck.

We are available should Liquidia believe that further meet and confer efforts would be productive. Thanks.

William C Jackson

GOODWIN

Goodwin Procter LLP
1900 N Street, NW
Washington, DC 20036
o +1 202 346 4216
m +1 202 270 6622
f +1 202 478 0819
WJackson@goodwinlaw.com

From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Friday, February 23, 2024 4:47 PM
To: Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; Jackson, William C <WJackson@goodwinlaw.com>; Dcarsten@mwe.com; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Adykhuis@mwe.com; aburrowbridge@mwe.com; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

EXTERNAL
Counsel,

I write to summarize the parties' meet and confer concerning UTC's anticipated PI motion, which was attended by Sanya Sukduang, Karen Keller, and Lauren Strosnick for Liquidia and William Jackson, Doug Carsten, and Michael Flynn for UTC.

The parties addressed the questions presented below.

Question 1, UTC recognized that it was seeking an injunction despite already having an injunction preventing the launch of Yutrepia. UTC offered to hold-back its proposed PI until after the Court decides Liquidia's Rule 60 Motion if Liquidia agreed to (a) grant UTC 5 days to decide to file a PI; and (b) if filed, not launch until the PI was resolved. **We presented this offer to Liquidia, but Liquidia cannot agree to this proposal**.

Question 2, UTC asserted that the APA action against the FDA seeks different relief than the proposed PI. Liquidia disagreed, indicating that the PI seeks to enjoin Liquidia from launching in PH-ILD and UTC's FDA action seeks to compel the FDA to revoke any approval of Yutrepia for PH-ILD and force Liquidia to refile. In short, both seek to enjoin Liquidia from launching Yutrepia in PH-ILD.

Questions 3-4, UTC asserted that it became aware of "recent" press release regarding Liquidia's anticipated launch and this "recent" notice was required to file a PI. UTC acknowledged, however, that the parties did conduct a meet and confer prior to December 25, 2023 (the exact date was December 6, 2023), where Liquidia provided notice, as expressly requested by UTC's counsel Mr. Jackson, that it would launch Yutrepia immediately upon FDA approval. UTC's counsel also agreed that during the December 6, 2023 meet and confer, Mr. Flynn suggested the parties contact the Court to address a PI briefing schedule.

Question 5, Liquidia asked if UTC would be amenable to postpone the UTC witness expert depositions in the NC trade secret case, to which UTC said it was. **Liquidia will submit a proposal to NC counsel shortly**.

Question 6, UTC indicated it intends to file its PI motion on Monday or Tuesday of next week.

Question 7, UTC has identified 2 experts (Dr. Nelson and Mr. Selck). Dr. Nelson is available for deposition on March 10 and Mr. Selck sometime thereafter. Liquidia is looking to see if those dates work.

Question 8, Liquidia requests an extension, until **April 5, 2024** to file its opposition, which UTC indicated it would consent to. UTC's requested two-weeks after Liquidia files its opposition to file its reply, to which Liquidia consents.

Thanks
Sanya

From: Flynn, Michael J. <mflynn@morrisnichols.com>
Sent: Thursday, February 22, 2024 12:50 PM
To: Sukduang, Sanya <ssukduang@cooley.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; William Jackson (Goodwin) <wjackson@goodwinlaw.com>; Douglas H. Carsten - McDermott Will & Emery LLP (dcarsten@mwe.com) <dcarsten@mwe.com>; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Art Dykhuis - McDermott Will & Emery LLP (adykhuis@mwe.com) <adykhuis@mwe.com>; Burrowbridge, Adam W. (MWE) <aburrowbridge@mwe.com>; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

[External]

Sanya,

We are available at 12:00 ET on Friday for a call and look forward to discussing your questions below.

Click to join meeting: https://meet.loopup.com/45xeX0IXC8

Or dial in:

US Toll Free: 1 877 304 9269
Passcode: **3023519661#**

Mobile Quick Join: tel://+18773049269,,3023519661#

MICHAEL J. FLYNN
Partner | Morris, Nichols, Arsht & Tunnell LLP
(302) 351-9661 Direct
mflynn@morrisnichols.com

From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Wednesday, February 21, 2024 9:51 PM
To: Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; William Jackson (Goodwin) <wjackson@goodwinlaw.com>; Douglas H. Carsten - McDermott Will & Emery LLP (dcarsten@mwe.com) <dcarsten@mwe.com>; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Art Dykhuis - McDermott Will & Emery LLP (adykhuis@mwe.com) <adykhuis@mwe.com>; Burrowbridge, Adam W. (MWE) <aburrowbridge@mwe.com>; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: [EXT] Re: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

Michael

We aren't available tomorrow, but can be Friday except between 3:00-4:00 pm, contingent upon UTC's ability to respond to the issues below .

During the call, we expect UTC to specifically address the following, and failure to do so will be raised with the Court:

1. Why UTC believes a PI is needed in this action given UTC's position, articulated as recently as yesterday, that the Court's 793 injunction cannot be lifted until the 793 claims are cancelled by the Director;

2. Why a PI is needed given UTC's complaint against the FDA that Yutrepia should not be launched;

3. UTC's delay, until February 21, 2024, to address a PI given the parties' specific discussion with you and William Jackson of a PI request prior to December 25, 2023 and Liquidia's request to address any potential PI briefing such that UTC does not force Judge Andrews to act expeditiously;

4. Why, despite filing a complaint 3 months ago concerning the '327 patent, UTC has waited to file a PI;

5. Why a PI is warranted given UTC's request for a 30 day extension of time to answer Liquidia's counterclaims based on proceedings in an unrelated litigation in NC and why Liquidia is also not entitled to rely on the schedule in NC to support a non-conflicting schedule;

6. The specific date UTC intends to file its PI motion and any declarations it may file in support;

7. The dates any UTC declarant is available for a deposition; and

8. The briefing schedule UTC proposes.

This above list is non-limiting and Liquidia may raise additional issues based on UTC's responses.

If UTC is prepared to fully address each issue above, Liquidia can be available on Friday except between 3:00-4:00 PM EST.

Thanks
Sanya

On Feb 21, 2024, at 6:07 PM, Flynn, Michael J. <mflynn@morrisnichols.com> wrote:

[External]

Counsel,

UTC intends to file a Motion for Preliminary Injunction to enjoin the launch of Yutrepia for treatment of pulmonary hypertension associated with interstitial lung disease upon the expiration of UTC's regulatory exclusivity on April 1, 2024, pending resolution of UTC's infringement claims for U.S. Patent No. 11,826,327 asserted in this action. We would like to discuss with you the timing of that motion and a briefing schedule.

Can you please let us know your availability **tomorrow**, **February 22,** for a call to discuss? We are available any time except 12-1 ET.

Thanks,
Michael

MICHAEL J. FLYNN
Partner | Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 351-9661 Direct
mflynn@morrisnichols.com | vcard | bio | www.morrisnichols.com

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS
CORPORATION,

Plaintiff,

Case No. 23-975

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant.

____

HIGHLY CONFIDENTIAL

ATTORNEYS' EYES ONLY

VIDEOTAPED DEPOSITION OF

FREDERIC SELCK, Ph.D.

Washington, D.C.
March 15, 2014

Reported by:
Misty Klapper, RMR, CRR, CSR
Job No.: 1111116

Friday, March 15, 2024
9:11 a.m. EDT

Held at the offices of:
GOODWIN PROCTER LLP
1900 N Street, N.W.
Washington, D.C. 20036
(202) 346-4000

Taken pursuant to notice, before Misty Klapper, Registered Professional Reporter, Certified Realtime Reporter, Certified Shorthand Reporter and Notary Public in and for the District of Columbia.

APPEARANCES:

ON BEHALF OF PLAINTIFFS:

KATHERINE CHENG, ESQUIRE
GOODWIN PROCTER LLP
1900 N Street, N.W.
Washington, D.C. 20036
(202) 346-4000
E-mail: katherinecheng@goodwinlaw.com

AND

ADAM W. BURROWBRIDGE, ESQUIRE
LILLIAN J. SPETRINO, ESQUIRE
McDERMOTT WILL & EMERY LLP
500 North Capitol Street, N.W.
Washington, D.C. 20001-1531
(202) 756-8000
E-mail: aburrowbridge@mwe.com
lspetrino@mwe.com

ON BEHALF OF DEFENDANT LIQUIDIA TECHNOLOGIES, INC.:

PHILLIP MORTON, ESQUIRE
SANYA SUKDUANG, ESQUIRE
JOHN HABIBI, ESQUIRE
COOLEY LLP
1299 Pennsylvania Avenue, N.W., Suite 700
Washington, D.C. 20004-2400
(202) 842-7800
E-mail: pmorton@cooley.com
ssukduang@cooley.com
jhabibi@cooley.com

ALSO PRESENT:

NORMAN REYNOLDS, VIDEO OPERATOR

C O N T E N T S

E X H I B I T S

P R O C E E D I N G S

VIDEO OPERATOR: We are now on the record. This begins the videotaped deposition of Frederic Selck, Ph.D., taken in the matter of United Therapeutic Corporation versus Liquidia Technologies, in the United States District Court for the District of Delaware, Case Number 23975.

Today's date is March 15th 2024. The time is 9:11. This deposition is being held at 1900 N Street, Northwest, Washington, D.C.

The court reporter is Misty Klapper on behalf of Magna Legal Services. The videographer is Norman Reynolds on behalf of Magna Legal Services. All counsel will be noted on the stenographic record.

Will the court reporter please swear in the witness.

MS. REPORTER: One moment.
FREDERIC SELCK, Ph.D.,
The witness herein, called for examination by counsel for the Defendant , having been duly sworn, was examined and testified as follows:
EXAMINATION BY COUNSEL FOR DEFENDANT
BY MR. MORTON:
Q. All right. Good morning.
A. Good morning.
Q. Please state your name for the record.
A. Fred Selck.
[redacted].
Q. All right. And I -- I take it you've been deposed before?
A. Yes.
Q. So you understand that you're

under oath and you have an obligation to answer my questions as truthfully and completely as possible?
A. Yes.
Q. If you don't understand any of my questions today, please ask me to clarify.
Can we do that?
A. Yes.
Q. All right. Is there any reason you can't give your best and complete testimony today?
A. No.
Q. All right. We've premarked Exhibit 1, which is a copy of your preliminary injunction declaration.
(Thereupon, Selck Exhibit 1 was marked for identification.)
MR. MORTON: I'll hand you a copy.
MS. CHENG: Thank you.
BY MR. MORTON:
Q. Could you please confirm this is

the declaration that you submitted in this case.
A. Yes, it is.
Q. How many times have you had your deposition taken before?
A. This is my tenth time.
Q. Okay. And is -- if you turn to Attachment A-1 of your Exhibit 1., that's a copy of your CV, right?
A. Yes, it is.
Q. All right. And if you turn to the second page of that Attachment A-1, there's a list of testimony there.
Is that a complete list of the cases in which you've provided testimony?
A. Yes.
Q. And how many of those cases were patent infringement cases?
A. None of these were -- were patent infringement cases.
Q. Have you ever given expert testimony on damages in a patent infringement

case?
A. Submitted an expert report rebutting a damages claim by Sanofi/Regeneron related to an injunction in Germany. And that report was submitted to the Munich court in -- in Germany.
Q. Okay. So you've never quantified damages in a U.S. patent infringement case?
A. I've -- I've quantified damages. As -- as far as offering expert testimony or testifying in court to those damages, I -- I have not done that.
Q. All right. Turn back to the first page of Attachment A-1. This reflects your -- our education and -- and prior work experience; is that correct?
A. That's correct.
Q. And looks like you've got several degrees in economics; is that right?
A. Yes.
Q. And you do not have a medical degree?

A. No, I do not.
Q. Do you have any type of life sciences degree?
A. I'm a -- my field as -- as -- as a Ph.D. economist was in health and -- and a -- and a subset of health is -- is life sciences.
Q. Okay. But you're not holding yourself out here as a -- a medical expert, right?
A. No.
Q. Or a scientific expert?
A. I do have graduate training in epidemiology and -- and biostatistics. So from that perspective, in -- in terms of quantification of -- or comparisons of things like clinical trial data and -- and things of that sort, I feel like I'm qualified to do. But I'm not a -- I'm not somebody that you would come and see and -- and get health care for.
Q. Fair enough.

Have you ever been involved in the treatment of pulmonary hypertension?
A. No.
Q. Or -- or pulmonary arterial hypertension?
A. No.
Q. Or pulmonary hypertension-interstitial lung disease?
A. No.
Q. Is this the first time you've worked on a matter on behalf of United Therapeutics?
A. Yes.
Q. Is this the first time you've worked on a matter involving any form of pulmonary hypertension?
A. Yes.
Q. And you're relying on Dr. Nathan for your understanding of the infringement and issues in this case?
MS. CHENG: Object to form.
THE WITNESS: With respect to

infringement, but in addition to that, I'm relying on Dr. Nathan for his descriptions on how prescribers or providers would view Yutrepia and -- and -- and Tyvaso.
BY MR. MORTON:
Q. Do you rely on Dr. Nathan for anything else?
A. No.
Q. When were you retained in this case?
A. Can't recall the -- the exact date, but the retention occurred in -- in middle of -- mid of -- middle of December.
Q. Middle of December of 2023?
A. '23.
Q. And when did you start work on your declaration in this case?
A. Immediately after -- after my retention.
Q. So you started work on your -- your declaration in December of 2023?

A. That's correct.
Q. And how much time did you spend preparing your declaration?
A. Do you mean in -- in terms of hours?
Q. Um-hmm.
A. I can't say for sure, given the -- I haven't looked specifically at -- at -- at the bills yet, but anywhere between 150 to -- to 200 hours.
Q. And you -- you -- you said you started work on this declaration in December.
Were there -- were you working on it consistently from December to February, when it was served?
A. Yes. And I should add in -- in conjunction with staff members who -- who reported to me in -- in -- in preparing this -- this declaration.
Q. Okay. Who are those staff members that reported to you?
A. Ryan Marsh. He's a Ph.D. at --

at my firm, Intensity.
Q. Um-hmm. Anyone else?
A. Anu Subramaniam, who's also a Ph.D.
Q. I -- I didn't catch that. Arun Subramaniam?
A. Anu.
Q. Anu?
A. Yes.
Q. Any Subramaniam. Okay. Thank you.
Anyone else?
A. And Kristyn Berretta. There were other staff members on that team as well, Ryan Sherrard, but Anu, Ryan Marsh and -- and Kristyn were the -- the principals on the team.
Q. How much time did your team spend on the declaration?
A. I haven't looked at the total number of hours that -- that -- that -- billed to the case, so I -- I -- I can't tell

you for sure.
Q. Okay. And I assume you're being compensated for your work on this declaration here?
A. Yes.
Q. Okay. And what -- what is your hourly rate that you're being compensated at?
A. Looking --
Q. Not sure I saw it in there. That's why I'm asking.
A. I believe --
Q. Maybe I overlooked it.
A. No, I -- I don't think it's in there. It's $1,050 an hour.
Q. Who drafted your declaration?
A. I drafted my declaration.
Q. You drafted every word in your declaration?
A. I had assistance from -- from my team, but I reviewed everything that was -- that was put into the declaration and I'm responsible for everything that's in my

declaration.
Q. And which portions of the declaration did you write?
A. I wrote the entire declaration.
Q. You wrote every word in the declaration?
A. I've had team members provide material to me as part of research tasks that I've given them. But as -- as it's put into the declaration, I review it and put it into my own words. So I -- I -- from my perspective, I've -- I've written my declaration.
Q. Are there any sections of the declaration you did not write?
A. No.
Q. So just so I'm clear, you wrote every word in this declaration? That's your testimony here?
MS. CHENG: Object to form.
THE WITNESS: I've reviewed material that was provided to me by my

team and, as it was put into the declaration, reviewed and refined every word that's -- that's in this declaration.
BY MR. MORTON:
Q. Are there any errors that you want to correct at this time in your declaration?
A. I think in the headers where I describe PCSK9 inhibitors, we may have transposed or I may have transposed the S and the C and -- and so I'd like to -- yes.
So if you look at paragraph 82, where -- where we have -- where I have PSCK9 inhibitors, that should be PCSK9 inhibitors.
Q. Fair enough. All right.
Looks like it may not only be in the header, but there's a few other places that have that typo.
A. I -- I apologize ahead of time.
Q. Any other errors that you want to correct in your declaration?

A. Not that I'm aware of.
Q. I see that you spoke to several people in support of your declaration; is that correct?
A. Yes.
Q. You spoke to Dr. Steven Nathan, correct?
A. Yes.
Q. And when did you speak to Dr. Nathan?
A. On February 9th 2024.
Q. Is that the only time you spoke to Dr. Nathan?
A. Yes.
Q. How long was your conversation with Dr. Nathan?
A. We had scheduled an hour. I don't know if we took the -- the whole hour, but -- but up to an hour.
Q. You spoke to Dr. Nathan for less than an hour, right?
A. Up to an hour.

Q. Was it closer to 30 minutes?
A. No, I -- I -- I think it was closer to an hour or up to an hour.
Q. All right. And was that a phone conversation or a videoconference?
A. Videoconference.
Q. Who else was present for that conversation?
A. I know United's counsel was -- was on that call. I don't know if I can recall everybody that was there. I know Katie Cheng was -- was there. The three individuals that I described on my team, Ryan Marsh, Anu Subramaniam and -- and Kristyn Berretta, were -- were also there.
Q. Anyone else you recall that was present for the conversation with Dr. Nathan?
A. I -- I don't want to misremember who was there on -- on United's counsel. The -- the -- the only one I know for sure was -- was Katie.
Q. You think there may have been

other counsel there?
A. Yes.
Q. Was there any in-house counsel from United Therapeutics there?
A. Not that I recall.
Q. Is there any written record of the conversation you had with Dr. Nathan?
A. I didn't take any notes.
Q. Did anybody take notes for you?
A. I'm not aware if anybody took notes for me.
Q. Did anybody provide you notes after the conversation with Dr. Nathan?
A. No.
Q. Did you have a copy of Dr. Nathan's declaration when you had the conversation --
A. No.
Q. -- with him?
Did you ever have a copy of Dr. Nathan's declaration?
A. The only time I saw Dr. Nathan's

declaration was after it was submitted.
Q. Okay. So before your declaration was submitted, you did not review Dr. Nathan's declaration; is that correct?
A. That is correct.
Q. And what did you discuss with Dr. Nathan during this conversation?
A. I was primarily interested in -- in getting background on treprostinil and more detail on pulmonary hypertension, as well as pulmonary arterial hypertension and -- and pulmonary hypertension-interstitial lung disease or -- I often refer to it as PH-ILD in my report.
There are also -- and -- and I might use this interchangeably as -- as we -- as we talk, but they're also referred to as -- as Group 1 or -- or Group 3 under the WHO classifications.
So I -- I -- we -- we talked a bit about that. And then we had a conversation as to whether he thought

providers and prescribers would -- would view Yutrepia and -- and Tyvaso DPI as interchangeable.
Q. Did you discuss anything else with Dr. Nathan?
A. I think that summarizes the entirety of our conversation.
Q. Okay. Just so the record's clear, you -- you referred to Group 1.
That refers to pulmonary arterial hypertension, or PAH, right?
A. That's correct.
Q. Okay. And then Group 3, that refers to pulmonary hypertension-interstitial lung disease, or PH-ILD?
A. That's correct.
Q. Okay. And we'll use -- probably end up using those terms interchangeably today, so -- but you understand that terminology?
A. Group 3 rolls -- rolls off the tongue a -- a little bit better.

Q. It does. I -- I -- I will agree with you on that.
And you also prepared a declaration in a matter involving the FDA; is that correct?
A. That's right.
Q. And -- and when did you start your work on that declaration?
A. The scope of charge for the FDA matter was exactly what the scope of charge was in -- in this declaration. And so the identification and -- and description of the harms, that work started in mid-December.
Q. Okay. When you say the scope of charge is the same, what do you mean by that?
A. My assignment.
Q. And -- and what do you view your assignment as here?
A. From a high level is to describe the -- the economic harms that United would -- would suffer as a result of Yutrepia's entry in the PH-ILD market.

Q. Is your declaration in the FDA matter the same as the declaration that you submitted in this matter?
A. There are modest differences between -- or modest changes between my -- my FDA declaration and -- and this one, in part because the -- what's being asserted as the mechanism for -- that the assertions with -- in -- in the FDA matter are different than they are in -- in this -- in this matter.
Q. I'll -- we'll unpack that a little bit.
So what you -- what are the changes that you made to this declaration for submission for the FDA declaration?
A. In this -- in this particular -- in this matter we're describing the harms that would -- that would result, absent a -- a -- a preliminary injunction as -- as the infringement allegations are -- are litigated.
In the FDA matter the allegations

are that the FDA improperly moved forward on the application for -- for PH-ILD or for Liquidia and, as a result, did not give United the opportunity to -- to assert a 30-month stay.
Q. Okay. But my question was about what are the changes that you made to the declaration. You told me what the difference was between the -- the cases.
What are the changes you made to the declaration for submission to the -- in the FDA matter?
A. In terms of -- in terms of the substance, the descriptions of -- of the matter itself are specific to -- to the two matters. And -- and those -- those were changes.
To the degree that the context of -- of the matters were different, you know, I -- I think that resulted in some modest changes between the -- the two declarations.

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But, for the most part, in terms of substance, the -- the declarations are the same.

Q. So if we go through the table of contents in your declaration here -- because I don't have a copy of the FDA declaration, so I don't know what you said in there -- what -- what are the difference -- or what sections are the same in the FDA matter as in this matter?

MS. CHENG: And, Counsel, you don't have the a copy of the FDA declaration that we could compare?

MR. MORTON: No, I don't. It wasn't provided to us.

THE WITNESS: No, I would -- I'd -- I'd -- I'd -- I'd hesitate to -- to offer an exact comparison without having the -- the FDA declaration in front of me.

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

BY MR. MORTON:

Q. You understand that United has other treprostinil products that predate Tyvaso, right?

A. Yes.

Q. And those go back to 2004 or earlier, right?

MS. CHENG: Object to form.

THE WITNESS: I -- I -- I can't recall exactly what -- what -- what year it goes back to.

BY MR. MORTON:

Q. [redacted]

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[redacted]

Q. Now, in preparation for your declaration, you didn't speak to any payors directly, correct?
A. That is correct.
Q. You didn't speak to any insurance companies, right?
A. Not -- not specifically to this matter. And even if I did, payors are quite reluctant to disclose any -- any negotiating posture or anything like that with -- with respect to manufacturers.
Q. You didn't discuss -- or you didn't -- strike that.
You didn't speak to any pharmacy benefit managers?

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A. Not for this matter, no.
Q. You didn't speak to anyone from Medicare or Medicaid?
A. No.
Q. You didn't speak to any other providers, other than Dr. Nathan; is that right?
A. That's correct.
Q. And you didn't speak to any patients that have been diagnosed with PAH or PH-ILD?
A. I didn't speak to any patients. I did review some YouTube videos that were available that showed patients taking either the nebulized or -- or -- or the dry powder formulations.
Q. What YouTube videos were those?
A. They were ones that I just Googled and -- and -- and found online.
Q. Are they cited in your materials considered in Attachment A-2?
A. No, they -- they weren't

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necessary for my opinion. It was just something that -- that did I out of curiosity.
Q. Okay. Besides the YouTube videos, is Attachment A-2 a complete list of the materials you considered in rendering your opinions in the declaration you've entered in this matter?
A. Yes, it is. And -- and -- and to be clear, the YouTube videos I didn't -- I didn't consider at all in -- in formulating my opinion.
Q. During any of your conversations

[redacted]

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[redacted]

Q. What did you do to prepare for your deposition here today?
A. I read my declaration; reviewed

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the -- the materials that -- that I considered; and I spent several hours with counsel yesterday.
Q. Okay. How -- how much time did you spend with counsel?
A. We were together from 10:00 in the morning until about 5:00 in the afternoon.
Q. How much time in total did you spend preparing for your deposition today?
A. In -- in between reviewing my declaration, time with counsel, and reviewing materials and, you know, discussing things with my team, anywhere between 25 or 30 hours.
Q. Did you speak with any United Therapeutics personnel in preparation for your deposition?
A. No.
Q. Did you speak with Dr. Nathan in preparation for your deposition?
A. No.

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MS. CHENG: Counsel, we've been going about an hour. Could we get a break --
MR. MORTON: Yeah, sure.
MS. CHENG: -- at a good point?
MR. MORTON: We can do that.
VIDEO OPERATOR: Going off the record at 10:15.
(Thereupon, a brief recess was taken.)
VIDEO OPERATOR: We're back on the record at 10:31.
BY MR. MORTON:
Q. Welcome back.
Were you involved in any discussions about your testimony during the break?
A. No.
Q. What is your understanding of Liquidia's Yutrepia product?
A. Yutrepia is a treprostinil-based dry powdered inhaler.

Q. Are there -- or how is Yutrepia different than Tyvaso DPI?
MS. CHENG: Object to form.
THE WITNESS: Based on my understanding, the particle shapes, what constitutes the powder within -- within -- within the capsules are different between Yutrepia and -- and Tyvaso. And I understand that the -- the device that's used to -- to contain the capsule is different from the one that's containing the Tyvaso capsule.
BY MR. MORTON:
Q. Any other differences that you're aware of between Yutrepia and Tyvaso DPI?
A. No.
Q. You agree that Yutrepia is not a generic version of the Tyvaso products, right?
A. I agree that Yutrepia was approved under the 505(b)(2) FDA approval

process.
Q. You agree that Yutrepia's a branded product, right?
A. Yes.
Q. You'd agree that Yutrepia is a strongly differentiated product from the Tyvaso products, right?
MS. CHENG: Object to form.
THE WITNESS: I disagree. Performed my -- my own comparisons where I looked at the proposed labels, assessed the addressable patient populations for -- for both products.
I also understand that they both share the same active ingredient. And I also understand from Dr. Nathan that he thinks it's likely that prescribers and providers will view these products as interchangeable.
BY MR. MORTON:
Q. You agree that Liquidia has preliminary approval from the FDA to -- to

launch Yutrepia for the PAH indication?
MS. CHENG: Object to form.
THE WITNESS: I understand that they have received tentative approval for -- for PAH from the FDA.
BY MR. MORTON:
Q. And -- and you'd agree that the injunction that's being sought in this case, that would not impact the launch of Yutrepia for at least the PAH indication, right?
MS. CHENG: Object to form.
THE WITNESS: I understand that the injunction that's being sought is specific -- specific to the PH-ILD indication.
BY MR. MORTON:
Q. Okay. So the injunction that is being sought in this case would not impact Liquidia's ability to launch Yutrepia for PAH, right?
MS. CHENG: Object to form.
THE WITNESS: I think even with

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a -- with an injunction in place for PH-ILD that Yutrepia would enter and -- and compete in the PAH indication space.
BY MR. MORTON:
Q. And you're not claiming there is any irreparable harm here based on Liquidia launching Yutrepia for the PAH indication, right?
MS. CHENG: Object to form.
THE WITNESS: I think the entry of Yutrepia in -- in PAH is going to affect United's behavior in the PH-ILD space and that there will be potential price erosion effects, even with Yutrepia's entry in -- in PAH.
BY MR. MORTON:
Q. When Yutrepia launches for the PAH indication, the only inhaled treprostinil products on the market will be the Tyvaso products and Yutrepia; is that correct?
A. In inhaled products, yes, that --

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that's my understanding. I just want to refer back and -- and confirm that -- there is one other product. I just want to confirm it's -- it's not inhalable in PAH.
I guess I -- I would say that Yutrepia and -- and Tyvaso would be the -- the only treprostinil-based inhalation products for -- for PAH.
Q. And if Yutrepia launches for the PH-ILD indication as well, Yutrepia and Tyvaso would be the only treprostinil-based inhalation products for PH-ILD on the market, right?
A. That's my understanding, yes.
Q. Now, you acknowledge in your report that there -- based on your conversation with Dr. Nathan that there can be challenges in diagnosing whether a patient has PAH or PH-ILD, right?
A. Yes, in particular, that for -- diagnosing pulmonary hypertension in general requires an invasive procedure called the

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right heart catheterization.
Q. But you agree that it can be challenging to diagnose whether a patient has PAH or PH-ILD?
A. My understanding is that from what Dr. Nathan indicated, the ability to differentiate between the two groups can be difficult for some patients.
Q. And -- and you rely on your conversations with Dr. Nathan for your understanding of the challenges of diagnosing patients with PAH or PH-ILD?
A. In addition to -- to Dr. Nathan, I have some background on -- on both -- some cited materials and background in the background in my report.
Q. But you don't have any of your own opinions about how patients are diagnosed with PAH or PH-ILD, right?
A. That's correct.
Q. You don't have any opinions about the -- I mean -- strike that.

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You don't have any of your own opinions about the challenges of diagnosing patients with PAH or PH-ILD, correct?
A. That's correct.
Q. And you don't have any of your own opinions about how medical professionals categorize patients with PAH or PH-ILD?
A. Only that medical professionals or providers generally categorize -- categorize these patients in -- in one group or the other.
Q. Is that your opinion, that medical professionals categorize patients in one group or another or is that -- you're just reciting what Dr. Nathan told you?
A. Excuse me. My understanding is that, you know, patients are diagnosed in -- in one group or -- or the other.
Q. And your understanding that patients are diagnosed in one group or the other, that comes from Dr. Nathan; is that right?

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A. And my reading of -- of -- of -- of the other materials that I cite in the background of my report.
Q. Now, you acknowledge in your report there are other products on the market that are used to treat PH-ILD but are not approved for PH-ILD, right?
MS. CHENG: Object to form.
THE WITNESS: Can you point to -- to me in my report where I say that?
BY MR. MORTON:
Q. You have a discussion of PDE-5 inhibitors as one example. Paragraph 151 is one place where you talk about that.
A. 151?
Q. Yes.
A. Yes.
Q. And your understanding is that these PDE-5 inhibitors, such as sildenafil, are described for PH-ILD off label?
MS. CHENG: Object to form.

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THE WITNESS: That's my understanding, yes.
BY MR. MORTON:
Q. And when Yutrepia's on the market and in the event there's an injunction entered here for PH-ILD, a physician could still prescribe Yutrepia for PH-ILD off label, right?
MS. CHENG: Object to form, foundation.
THE WITNESS: So the -- the use of other products or off-label use of other products is -- you know, my health economist, whose dissertation was -- was studying physician and -- and prescriber behaviors.
If -- if there are no other treatments available, it's not unusual to -- to see physicians try therapies that -- that aren't necessarily indicated for a particular disease.
However, the introduction of

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Tyvaso is the first product that's been shown to -- to -- to be safe and effective in -- in -- in the treatment of PH-ILD. And I think the available of a -- of an on-label treatment that has demonstrated safety and efficacy for the treatment of -- of ILD incentivizes physicians to prescribe Tyvaso for -- for PH-ILD, as opposed to a -- to -- to an off-label alternative.
BY MR. MORTON:
Q. All right. Well, my -- my question was much simpler. I'm -- all I'm asking is a physician -- if Yutrepia was on the market, a physician could prescribe -- strike that.
If Yutrepia was on the market and the injunction was entered in the -- that's being sought in this case for PH-ILD, a physician could still prescribe Yutrepia for PH-ILD off label if they chose to do so?

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MS. CHENG: Object to form, asked and answered, foundation, outside the scope.
THE WITNESS: Not necessarily. One of the features of this particular market, I think one of the idiosyncrasies of this particular market, is you have payors and PBMs who are held to having products on their formularies that are consistent with their label. And the only product, if there was an injunction in place, that would be available in the formulary for the treatment of PH-ILD would be Tyvaso D -- Tyvaso.
BY MR. MORTON:
Q. Okay. My -- my question wasn't about the PBMs or the payors. My question was just about the doctors.
Could the doctor prescribe Yutrepia for PH-ILD off label if the injunction was entered in this case?

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MS. CHENG: Object to form, asked and answered, foundation, outside the scope.

THE WITNESS: The -- a -- a physician is able to prescribe, you know, according to -- to what their practice is. But in practicality, in writing a prescription for Yutrepia for an indication for which it's not indicated would likely be rejected by the payor or the PBM.

BY MR. MORTON:

Q. Given that the -- strike that.

Given that the Tyvaso products have been approved for PH-ILD, have doctors stopped using PDE-5 inhibitors like sildenafil for PH-ILD?

MS. CHENG: Object to form, foundation, outside the scope.

THE WITNESS: I -- I -- I haven't evaluated, nor was it my assignment to -- to assess the -- the

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level of off-label use of -- of other products for -- for PH-ILD.

I do know that with the introduction of -- of Tyvaso for -- for PH-ILD, the growth in -- in -- the use of Tyvaso for that indication has been substantial and is an indication of physicians and -- and other prescribers' desire for -- for treatment for -- for -- for this indication.

BY MR. MORTON:

Q. Do you know whether Dr. Nathan still uses sildenafil for PH-ILD?

A. I'm not aware.

Q. If the -- if Yutrepia's device were easier to use for PH-ILD patients than the Tyvaso DPI device, wouldn't that be another reason for doctors to use Yutrepia off label for PH-ILD?

MS. CHENG: Object to form, foundation, outside the scope,

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incomplete hypothetical.

THE WITNESS: I haven't seen any -- any indication or any kind of head-to-head comparisons demonstrating that Yutrepia is -- is easier or -- or better to use or superior in any fashion to -- to -- to Tyvaso dry powder formulation.

BY MR. MORTON:

Q. So throughout your report you reference a, quote, PH-ILD market. But I -- I didn't see a definition for that clearly.

Could you please tell me what your definition of the PH-ILD market is.

A. PH-ILD market consists of patients who have interstitial lung disease and also have pulmonary hypertension and who would be an eligible population for the treatments that are available for -- for PH-ILD.

Q. Did you use any test to define the PH-ILD market?

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A. What -- what -- what -- what kind of tests are -- are you referring to?

Q. Well, for example, I -- I'm familiar with a test called the -- the SSNIP test.

Are you familiar with that test?

A. I'm familiar with the SSNIP test.

Q. Okay. Did you use the SSNIP test to define the PH-ILD market?

A. For -- for -- for the purposes of -- of identifying the addressable population or -- or the addressable market in -- in -- in this particular instance, I didn't think a -- a -- a SSNIP test was -- was necessary.

Q. Did you apply -- well, strike that.

What -- what is your understanding of the SSNIP test?

MS. CHENG: Objection, outside the scope.

THE WITNESS: As a -- as -- as

a general matter, SSNIP stands for
the -- a -- a small, but
significant -- or significant
sustainable increase in price to
evaluate whether the market would
tolerate that increase in price.
And again, I'm -- I'm -- I'm
probably mangling the -- the -- the
definition, but it's a way of
evaluating whether there are
elasticities in the background that
cause switching or substitution.
BY MR. MORTON:
Q. And -- and just so the record's
clear, the SSNIP test is SSNIP, correct?
A. Correct.
Q. But you didn't use any test like
the SSNIP test or any -- any other economics
test to define the market here?
MS. CHENG: Object to form.
THE WITNESS: For -- for -- for
the purposes of my opinion and from --

from a -- from a -- from a high level,
the market is already well-defined
in -- in part because the market
consists of observable
characteristics. And -- and the
observable characteristics in this
case are sufferers of interstitial
lung disease who also have pulmonary
hypertension.
BY MR. MORTON:
Q. You also reference a PAH market
in your report. How are you defining the PAH
market?
A. In essentially the same fashion.
These are observable characteristics amongst
patients who suffer from pulmonary arterial
hypertension.
Q. So like the PH-ILD market, you're
defining the PAH market as the -- the
patients that have either PAH or PH-ILD,
right?
MS. CHENG: Object to form,

mischaracterizes --
BY MR. MORTON:
Q. That -- yeah, let me redo that
question.
So you're defining the -- the --
the PAH market in your declaration as the
group of patients that have observable
characteristics of pulmonary arterial
hypertension, right?
MS. CHENG: Object to form.
THE WITNESS: I'm defining it
as -- as patients that have the
condition that could or -- that could
be diagnosed using right heart
catheterization as -- as having
pulmonary arterial hypertension.
MS. REPORTER: Would you repeat
the end of that answer?
THE WITNESS: Sorry. Pulmonary
arterial --
MS. REPORTER: No.
THE WITNESS: Right -- right

heart catheterization. Sorry.
[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

MR. MORTON: All right. Why don't we take a break.

VIDEO OPERATOR: Going off the record at 12:28.

(Thereupon, at 12:28 p.m. EDT, a lunch recess was taken.)

AFTERNOON SESSION (1:13 p.m. EDT)

VIDEO OPERATOR: We're back on the record at 13:13.

BY MR. MORTON:

Q. Welcome back.

A. Thank you.

Q. Were you involved in any discussions regarding your testimony during the break?

A. No.

[redacted]

[redacted]

[redacted]

[redacted]

BY MR. MORTON:
Q. All right. I'd like to turn to Section 5.5 of your report, which starts at page 68.
Let me know when you're there.
A. I'm there.
Q. And in -- in this section you are discussing your opinions about Liquidia's ability to compensate United for any damages in this case; is that right?
A. What I'm describing is a -- is Liquidia's limited ability to compensate United, properly compensate United.
Q. Yeah, when -- when I read this section, it -- you appear to discuss the sales of PH-ILD and whether Liquidia could compensate United for the sales of PH-ILD that are allegedly lost. But I didn't see you have any discussion in here about sales of PAH.

Did -- did you talk -- did you consider that at all in your consideration of whether Liquidia could pay any damages award in this case?
MS. CHENG: Object to form.
THE WITNESS: From a high level, from a -- from an economics perspective, one of the things that express the expected value of the firm is its market capitalization. So Liquidia is a publicly traded firm, has shares that are traded and -- and have a -- a price and a market capitalization that we can -- that we can capture.
And, in essence, that market capitalization captures what investors think is both the -- well, what -- what they think the value of -- of Liquidia's enterprise is moving forward.
That implicitly captures

expectations regarding PAH sales.
BY MR. MORTON:
Q. But did you consider the revenues that Liquidia would obtain from PAH sales once it is permitted to launch that?
MS. CHENG: Object to form.
THE WITNESS: I -- I considered PAH sales, along with expectations of other products and -- and their -- and their revenue performance in -- in Liquidia's portfolio by using Liquidia's market capitalization as a -- an indicator for that.
BY MR. MORTON:
Q. So you only used the market capitalization. You didn't take into account any revenues that Liquidia may earn from selling Yutrepia for the PAH indication?
MS. CHENG: Object to form, mischaracterizes testimony.
THE WITNESS: I did -- I did consider PAH revenues, as well as --

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and -- and really, the -- the correct financial metric to -- to apply in this particular instance is profits from the portfolio products that Liquidia has and -- and potentially will -- will bring to market and Liquidia's market capitalization can in some ways -- and -- and -- and to be clear, there are limitations to this, but can in some ways be a reflection of what that value is.

BY MR. MORTON:

Q. Okay. Besides Liquidia's market capitalization on February 12th 2024, can you point me to anywhere in your report where you're discussing Liquidia's revenues for Yutrepia for the PAH indication?

A. Well, what -- what I'm showing here is even under conservative assumptions with respect to market share and -- and price erosion in the ILD market as a result of Yutrepia's entry, under those conservative

assumptions, it would just take a -- a short period of time of that entry to exceed Liquidia's market capitalization, which, in turn, captures all these streams of revenues.

But from a forward-looking what would revenues be for -- for PAH for -- for Liquidia, I didn't consider that specifically as part of this analysis.

Q. Okay. And you didn't consider specifically Liquidia's profits on a going-forward basis for PAH?

MS. CHENG: Object to form.

THE WITNESS: My calculation and my approach to this assumes that the market capitalization captures the expectations of not just profits, but -- profits from PAH, but also profits from all the other potential portfolio products for Liquidia.

BY MR. MORTON:

Q. Okay. But it's -- you didn't consider on a stand-alone basis Liquidia's

profits for selling Yutrepia for PAH?

A. For the purposes of this calculation, I -- I did not.

[redacted]

Q. You understand the injunction that is sought here that you're providing a declaration about, that -- that injunction is only through the conclusion of the trial in this case, right?

MS. CHENG: Object to form.

THE WITNESS: I understand that the cumulative loss that occurs could be constrained by whatever outcome

occurs as a -- as a result of this litigation.

BY MR. MORTON:

Q. Okay. But the injunction that we're focused on right now for the purposes of your declaration, that's from the time period from when Yutrepia launches for the PH-ILD indication to trial and the decision in the trial of this case, right?

MS. CHENG: Object to form.

THE WITNESS: Yes, I -- I -- I don't know exactly when the -- the preliminary injunction would expire, for lack of a better term, but it would be -- that would limit the -- the cumulative losses that -- that are projected here.

BY MR. MORTON:

Q. So it would only be for that time period between the launch of Yutrepia for PH-ILD and whenever the preliminary injunction expires in this case, right?

A. Conditional on whatever outcomes extend beyond that. You know, obviously there's a -- there -- there's uncertainty with whether there will be, you know, depending upon the outcome, other injunctions or things of that sort. But that -- that could be a constraint, yes.

Q. Or the outcome could be that my client wins and there is no injunction, right?

A. That's correct.

Q. Okay. So the time period of potential loss that you're addressing with this preliminary injunction is from the time that Yutrepia launches for the PH-ILD indication until the preliminary injunction expires, right?

A. That's -- that's one -- one way to limit the -- the projection in this case, yes.

Q. Okay. So the amount of loss that Liquidia might need to compensate United for

would be limited to the revenues that are allegedly lost from the time that Yutrepia launches for the PH-ILD indication until the preliminary injunction expires, right?

MS. CHENG: Object to form.

THE WITNESS: I would characterize it a little -- a little bit differently.

So -- so, again, I -- I want to revisit specifically the -- that the purpose of -- of the calculation, one, is -- is it doesn't encompass all the loss. As I describe in my report, there are multiple avenues of -- of harms that United will -- will suffer.

So, you know, this, again, just kind of illustrates, you know, under -- under a set of assumptions what -- what those numbers could be.

But the point of -- of the -- of the calculation itself was to indicate even -- even with the

relatively short period of time, from 2024 to 2025 and even -- even through potentially 2026, under -- under these broad assumptions and -- and not really encompassing all the -- all the sources of loss to United, I still -- we still end up with a cumulative present value of the loss of north of $1.4 billion.

BY MR. MORTON:

Q. During what time period is that $1.4 billion calculation?

A. From 2024 through 2026.

Q. Okay. Well, you understand the trial in this case has been scheduled for June 23rd of 2025?

A. Yes.

Q. Okay. So that -- that's when there would be some sort of decision that would result in the preliminary injunction being lifted or, you know, some other injunction being entered, right?

MS. CHENG: Object to form, incomplete hypothetical.

THE WITNESS: It -- it's -- it's conditioned on a variety of different things, including if the -- if the trial date holds.

So there -- you know, I'm not setting a definitive line here as -- as to what -- what I think that constraint is going to be. Again, I'm trying to illustrate that even if you took into account the entire market capitalization of Liquidia now, given conservative assumptions with respect to market share and price erosion, those losses could be substantial.

It would comprise -- even if you were to limit it to just one or two years, would comprise a significant proportion of Liquidia's market capitalization.

BY MR. MORTON:
Q. Okay. But then Liquidia would still be able to sell Yutrepia for the PAH indication going into the future, right, because there would be no limitation on that once Yutrepia is permitted to launch for PAH, right?
MS. CHENG: Object to form, incomplete hypothetical.
THE WITNESS: It's hard to say what -- what Liquidia is going to be able to do in the event that it does have to compensate, even under conservative assumptions, for damages to -- to United. And that might include insolvency for -- for Liquidia.
BY MR. MORTON:
Q. Setting that aside, I -- I just want to get to the basic point that you agree that Yutrepia could be sold for the PAH indication going into the future and Liquidia

could continue to accrue revenues and earn profits on those sales, right?
MS. CHENG: Same objections, asked and answered.
THE WITNESS: Yeah, I -- I -- I guess I wasn't clear. That assumes Liquidia's ability to continue to finance its -- its PAH production operations, given its exposure to a -- a substantial liability of several hundreds of millions of dollars in an initial period of time. So that's why I mentioned the -- the insolvency point.
BY MR. MORTON:
Q. Okay. Do you have any understanding of what type of revenues Liquidia may be able to earn on the sale of PAH-indicated Yutrepia?
A. It would be some fraction of -- of revenues that are currently generated by United through its Tyvaso franchise for PAH.

Q. But do you know how much those revenues would be?
A. It depends on a variety of different factors. The aggressiveness of -- of Liquidia's discounting of its -- of its Yutrepia product as it competes head to head with Tyvaso in -- in PAH has a direct relationship on the net revenues that it's going to receive.
On the flip side of that, based on that aggressive or -- or not aggressive stance with -- with respect to discounting, is Liquidia's market share that it's able to capture in -- in PAH as -- as a result of that competition.
So it's hard to say exactly, you know, what -- what that percentage is going to be.
Q. Okay. And you haven't considered here what revenues Liquidia may be able to earn for selling Yutrepia for PAH, right?
MS. CHENG: Object -- object to

form, asked and answered, mischaracterizes testimony.
THE WITNESS: So what I would -- again, just to summarize, you know, what -- what I've done here, is -- is just illustrate how quickly a lower bound or what one could consider a lower bound of damages would be, making conservative assumptions.
That doesn't include all the other harms that -- that United will suffer as a result of Yutrepia entry that become a substantial fraction of Liquidia's market capitalization, which in turn is, in some respects, a reflection of the market's expectation for Liquidia's ability to earn profits not just from PAH, but from its other --
BY MR. MORTON:
Q. Okay. And you --
A. -- portfolio products.

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BY MR. MORTON:
Q. And you haven't attempted to protect what revenues Liquidia may earn from selling Yutrepia for the PAH indication, have you?
MS. CHENG: Object to form.
THE WITNESS: As I've indicated before, it's -- it's dependent upon a variety of different factors and ones that we haven't observed yet. That includes Liquidia's stance with -- with respect to discounting Yutrepia as part of its efforts to -- to capture market share; its success in -- in being able to capture that market share.
There's -- there's a lot -- there's a lot of moving parts that go into what the expected revenues are going to be.
BY MR. MORTON:
Q. I'm just -- I asked for a simple

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question.
Have you attempted to project what the revenues would be for Liquidia selling PAH or selling Yutrepia for the PAH indication?
MS. CHENG: Object to form.
BY MR. MORTON:
Q. Yes or no?
MS. CHENG: Same objection.
THE WITNESS: For all -- for all the reasons that I've described, I've -- I've not done a projection.
BY MR. MORTON:
Q. Okay. And you haven't done a projection of Liquidia's profits for the sale of Yutrepia for the PAH indication, correct?
A. For all the reasons that I've described, you know, the -- not knowing, you know, the -- the different parameters that kind of go into estimating those -- those type -- those type of projections, I haven't -- I haven't done a projection of --

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of -- of what those sales might be.
Q. My question was about profits, but --
A. Excuse me, for -- for profits.
Q. Gotcha. Okay.
All right. Earlier you mentioned that you had other forecasts for Tyvaso sales when I was asking you about the 2021 or 2022 projections.
What -- what documents were those in, because I haven't seen those?
A. I -- I thought that there were projections in -- in either United's 10-Ks or in some of the slide decks that describe United's marketing strategy. But I would -- I would have to have them in front of me in order for me to point them out.
Q. Okay. You don't recall right now which document that was in?
A. Not -- not immediately.
Q. Want to talk a little bit about your section on first mover advantages,

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Section 4.4. It starts on page 49.
A. Okay.
Q. You there?
A. Yes.
Q. Okay. Thank you.
So you claim that United will lose its first mover advantage if Yutrepia is on the market for the PH-ILD indication; is that right?
A. My understanding is Tyvaso is -- is the first indicated treatment for -- for PH-ILD and -- and as a result, United is a -- is a first mover in that space.
Q. Okay. Did you take into account any impact on United's first mover advantage due to Yutrepia being on the market for the PAH indication?
MS. CHENG: Object to form.
THE WITNESS: I wasn't asked to -- to examine the -- the -- the PAH market or the effect of -- of Yutrepia on -- on the PAH market.

BY MR. MORTON:
Q. Do you agree that United claims that it's built substantial brand recognition through its investments in the Tyvaso products prior to obtaining approval for the PH-ILD indication?
A. Where do -- where do you see that?
Q. I was summarizing what -- what you said in your report.
Well, you do talk about brand recognition in your report, don't you? Like it -- for example, paragraph 97 you mention it. 96 also talks about the brand name of Tyvaso.
A. Think your question related to brand recognition within the -- within the PAH market; am I -- is -- is that correct?
Q. It -- my question was about you contend that United has built substantial brand recognition through its investments in the Tyvaso products prior to obtaining

approval for the PH-ILD indication; is that right?
MS. CHENG: I say, you know, through its investments in the Tyvaso products in -- in paragraph 95. I say, Through its investments in -- in the Tyvaso products, United has engaged in an effort to increase its brand recognition for the Tyvaso products among both physicians and patients.
BY MR. MORTON:
Q. Yeah. And United has long been known as one of the most significant suppliers of therapies to treat pulmonary hypertension, right?
MS. CHENG: Object to form and foundation.
THE WITNESS: I don't know if I -- if I say that to -- if -- if you have an area in my report where I say that, I'm -- I'm happy to review it.

BY MR. MORTON:
Q. Well, we've talked about today how United's been in -- in the market for almost 20 years in various treatments for pulmonary hypertension, right?
MS. CHENG: Object to form, mischaracterizes testimony.
THE WITNESS: I think we -- we -- we specifically discussed that United had introduced a Tyvaso nebulizer in 2009 and has had that product on the -- on the market since 2009 and then introduced Tyvaso dry powdered inhalation form in -- in 2022. And I think we discussed how they've -- they had other products on the market prior to that.
But that's -- whether that's resulted in brand recognition for -- for United, I don't think I -- I -- I state anything specifically in my report about that.

BY MR. MORTON:
Q. Okay. So you didn't take into account the other therapies that United has, like Remodulin or Orenitram for PAH?
MS. CHENG: Object to form.
THE WITNESS: No. And -- and -- and with respect to the -- the -- the first mover advantage I describe here, as I understand it, both in my conversations with Dr. Nathan and Mr. Bottorff, the physicians that engage in treatment for PH-ILD are in many ways distinct from the physicians that -- that treat PAH.
So even if there were brand recognition within the PAH market, it's not clear to me that that carries over and has the same effect for the physicians or -- or prescribers that would -- that would prescribe treatment for PH-ILD.

BY MR. MORTON:
Q. All right. Setting -- setting that aside, are you contending that all of the first mover advantage that United had built over the years is going to be disrupted or eliminated based on a small startup entrant that you claim could go bankrupt?
MS. CHENG: Object to form.
THE WITNESS: I think innovators like United who expend considerable resources to develop new products and -- and enter into a -- a new space that is populated by providers that may not have been exposed to their -- to their products before in many -- in many respects, I expect to be recognized for that innovation and -- and -- and for those efforts.
And that could be short-circuited by -- by premature entry by another entrant, small or

otherwise.
BY MR. MORTON:
Q. So you're saying that Liquidia, a -- a small startup entrant, is going to disrupt United's first mover advantage in the treprostinil market?
MS. CHENG: Object to form.
THE WITNESS: To be clear, it's -- it's not the treprostinil market. It's -- it's the market for -- for PH-ILD patients, which, again, as I understand it, is -- is distinct from the physicians and prescribers that treat PAH patients.
And because they're -- they're different and distinct, there's no reason to assume that the PH-ILD physicians are aware of the innovator status that -- that United has.
BY MR. MORTON:
Q. And -- and your understanding of the distinction that you're drawing between

the physicians and prescribers of P -- for PAH patients and PH-ILD patients, you got that understanding from Dr. Nathan, correct?
MS. CHENG: Object to form, mischaracterizes testimony.
THE WITNESS: I got it from both Dr. Nathan and -- and Mr. Bottorff. I also understand that from United's marketing documents as well.
BY MR. MORTON:
Q. All right. I think I'm wrapped up.
MS. CHENG: No questions.
MR. MORTON: Okay. We're done.
VIDEO OPERATOR: Okay. Stand by. This concludes today's deposition.
We're off the record at 13:51.
(Thereupon, signature having not been waived, at 1:51 p.m. EDT the deposition concluded.)

CERTIFICATE OF DEPONENT

I, Frederic Selck, Ph.D., do hereby certify that I have read the foregoing pages, which contain a correct transcript of the answers given by me to the questions propounded to me herein, except for changes, if any, duly noted on the enclosed errata sheet.

____
FREDERIC SELCK, Ph.D.

Sworn and subscribed to before me this ___ day of ______________, 2024.

My commission expires: Notary Public:

______________________ _________________________

CASE: United Therapeutics Corporation v.
Liquidia Technologies, Inc., et al.
DEPOSITION OF: Frederic Selck, Ph.D.
TAKEN: March 15, 2024

PAGE	LINE	ERROR	CORRECTION	REASON

____
FREDERIC SELCK, Ph.D.

CERTIFICATE OF NOTARY

I, MISTY KLAPPER, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was taken by me in shorthand and thereafter reduced to typewriting by me; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

____
Misty Klapper, RMR, CRR, CSR
Notary Public

EXHIBIT 5

Minn, Robert

From:	Flynn, Michael J. <mflynn@morrisnichols.com>
Sent:	Thursday, February 22, 2024 9:50 AM
To:	Sukduang, Sanya
Cc:	Davies, Jonathan; kkeller@shawkeller.com; Nate Hoeschen; William Jackson (Goodwin); Douglas H. Carsten - McDermott Will & Emery LLP (dcarsten@mwe.com); Cheng, Katherine; Art Dykhuis - McDermott Will & Emery LLP (adykhuis@mwe.com); Burrowbridge, Adam W. (MWE); Lobel, Louis; Romeo, Eric; Mhkim@mwe.com; z/Liquidia v UTC 308970-201
Subject:	RE: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

[External]

Sanya,

We are available at 12:00 ET on Friday for a call and look forward to discussing your questions below.

Click to join meeting: https://meet.loopup.com/45xeX0IXC8

Or dial in:
US Toll Free: 1 877 304 9269
Passcode: **3023519661#**

Mobile Quick Join: tel://+18773049269,,3023519661#

MICHAEL J. FLYNN
Partner | Morris, Nichols, Arsht & Tunnell LLP
(302) 351-9661 Direct
mflynn@morrisnichols.com

From: Sukduang, Sanya <ssukduang@cooley.com>
Sent: Wednesday, February 21, 2024 9:51 PM
To: Flynn, Michael J. <mflynn@morrisnichols.com>
Cc: Davies, Jonathan <jdavies@cooley.com>; kkeller@shawkeller.com; Nate Hoeschen <nhoeschen@shawkeller.com>; William Jackson (Goodwin) <wjackson@goodwinlaw.com>; Douglas H. Carsten - McDermott Will & Emery LLP (dcarsten@mwe.com) <dcarsten@mwe.com>; Cheng, Katherine <KatherineCheng@goodwinlaw.com>; Art Dykhuis - McDermott Will & Emery LLP (adykhuis@mwe.com) <adykhuis@mwe.com>; Burrowbridge, Adam W. (MWE) <aburrowbridge@mwe.com>; Lobel, Louis <LLobel@goodwinlaw.com>; Romeo, Eric <ERomeo@goodwinlaw.com>; Mhkim@mwe.com; z/Liquidia v UTC 308970-201 <zLiquidiavUTC308970201@cooley.com>
Subject: [EXT] Re: UTC/Liquidia (23-975) - Meet & Confer on Prelim. Inj. Motion

Michael

We aren't available tomorrow, but can be Friday except between 3:00-4:00 pm, contingent upon UTC's ability to respond to the issues below .

During the call, we expect UTC to specifically address the following, and failure to do so will be raised with the Court:

1. Why UTC believes a PI is needed in this action given UTC's position, articulated as recently as yesterday, that the Court's 793 injunction cannot be lifted until the 793 claims are cancelled by the Director;

2. Why a PI is needed given UTC's complaint against the FDA that Yutrepia should not be launched;

3. UTC's delay, until February 21, 2024, to address a PI given the parties' specific discussion with you and William Jackson of a PI request prior to December 25, 2023 and Liquidia's request to address any potential PI briefing such that UTC does not force Judge Andrews to act expeditiously;

4. Why, despite filing a complaint 3 months ago concerning the '327 patent, UTC has waited to file a PI;

5. Why a PI is warranted given UTC's request for a 30 day extension of time to answer Liquidia's counterclaims based on proceedings in an unrelated litigation in NC and why Liquidia is also not entitled to rely on the schedule in NC to support a non-conflicting schedule;

6. The specific date UTC intends to file its PI motion and any declarations it may file in support;

7. The dates any UTC declarant is available for a deposition; and

8. The briefing schedule UTC proposes.

This above list is non-limiting and Liquidia may raise additional issues based on UTC's responses.

If UTC is prepared to fully address each issue above, Liquidia can be available on Friday except between 3:00-4:00 PM EST.

Thanks
Sanya

On Feb 21, 2024, at 6:07 PM, Flynn, Michael J. <mflynn@morrisnichols.com> wrote:

[External]

Counsel,

UTC intends to file a Motion for Preliminary Injunction to enjoin the launch of Yutrepia for treatment of pulmonary hypertension associated with interstitial lung disease upon the expiration of UTC's regulatory exclusivity on April 1, 2024, pending resolution of UTC's infringement claims for U.S. Patent No. 11,826,327 asserted in this action. We would like to discuss with you the timing of that motion and a briefing schedule.

Can you please let us know your availability **tomorrow**, **February 22,** for a call to discuss? We are available any time except 12-1 ET.

Thanks,
Michael

MICHAEL J. FLYNN
Partner | Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
P.O. Box 1347

Wilmington, DE 19899-1347
(302) 351-9661 Direct
mflynn@morrisnichols.com | vcard | bio | www.morrisnichols.com

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EXHIBIT 6

US011826327B2

(12) **United States Patent**
Peterson et al.

(10) **Patent No.: US 11,826,327 B2**
(45) **Date of Patent: Nov. 28, 2023**

(54) **TREATMENT FOR INTERSTITIAL LUNG DISEASE**

(71) Applicant: **United Therapeutics Corporation**, Silver Spring, MD (US)

(72) Inventors: **Leigh Peterson**, Hillsborough, NC (US); **Peter Smith**, Durham, NC (US); **Chunqin Deng**, Chapel Hill, NC (US)

(73) Assignee: **United Therapeutics Corporation**, Silver Spring, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 263 days.

(21) Appl. No.: **17/233,061**

(22) Filed: **Apr. 16, 2021**

(65) **Prior Publication Data**

US 2021/0330621 A1 Oct. 28, 2021

Related U.S. Application Data

(60) Provisional application No. 63/011,810, filed on Apr. 17, 2020, provisional application No. 63/160,611, filed on Mar. 12, 2021.

(51) **Int. Cl.**
A61K 31/192 (2006.01)
A61P 9/12 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/192*** (2013.01); ***A61K 9/0075*** (2013.01); ***A61K 9/0078*** (2013.01); ***A61P 9/12*** (2018.01)

(58) **Field of Classification Search**
CPC A61K 31/192
See application file for complete search history.

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Primary Examiner — Paul V Ward
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Methods of treating of interstitial lung disease, reducing pulmonary function decline in a subject with interstitial lung disease (ILD), and increasing forced vital capacity (FVC) in a subject suffering from ILD are provided, wherein the methods include administration of treprostinil.

19 Claims, 15 Drawing Sheets

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Figure 1

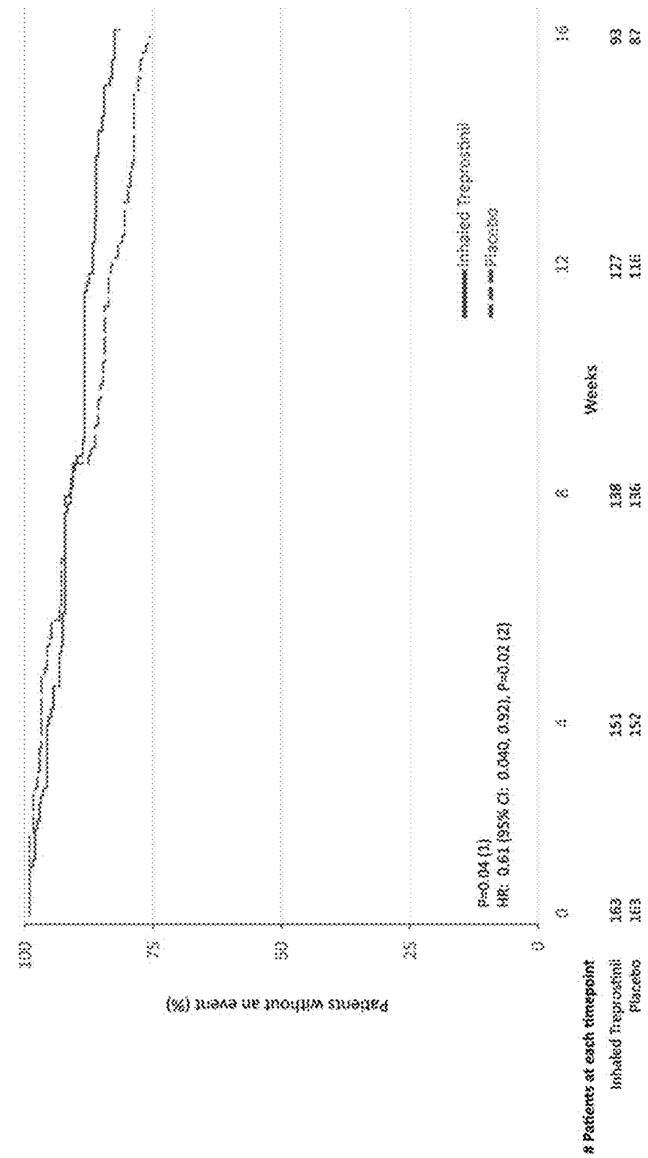

Patients without an event (%)
100
75
50
25
0
0
4
8
12
16
Weeks
Inhaled Treprostinil
Placebo
P=0.04 (1)
HR: 0.61 (95% CI: 0.040, 0.92), P=0.02 (2)
Patients at each timepoint
Inhaled Treprostinil
Placebo
163
163
151
152
138
136
127
116
93
87

Figure 2

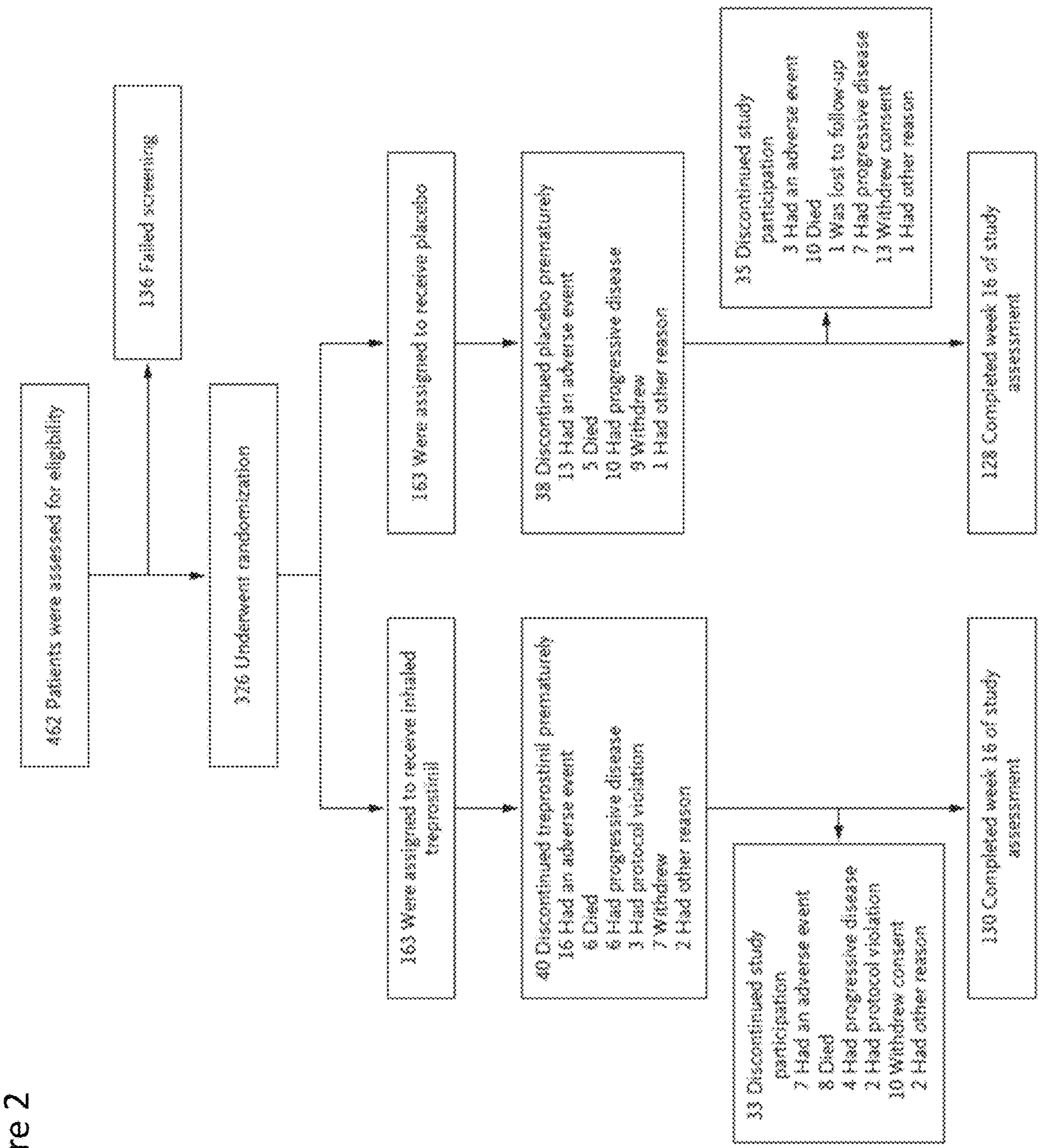
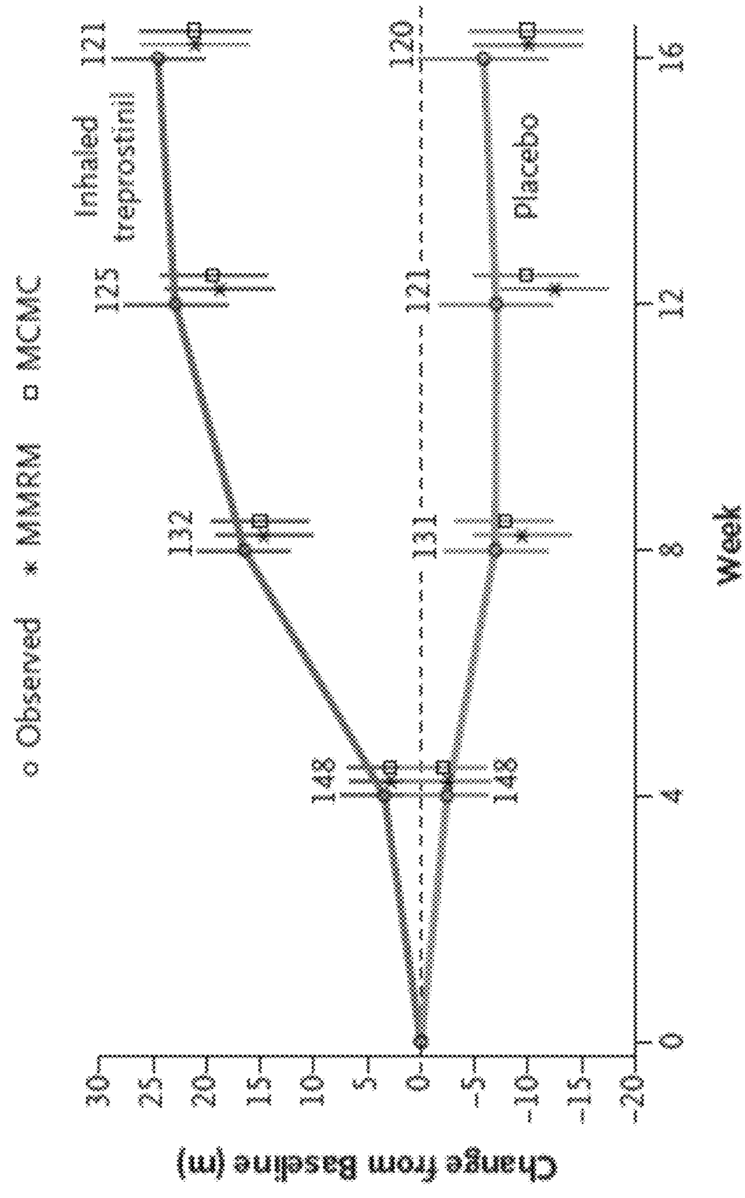
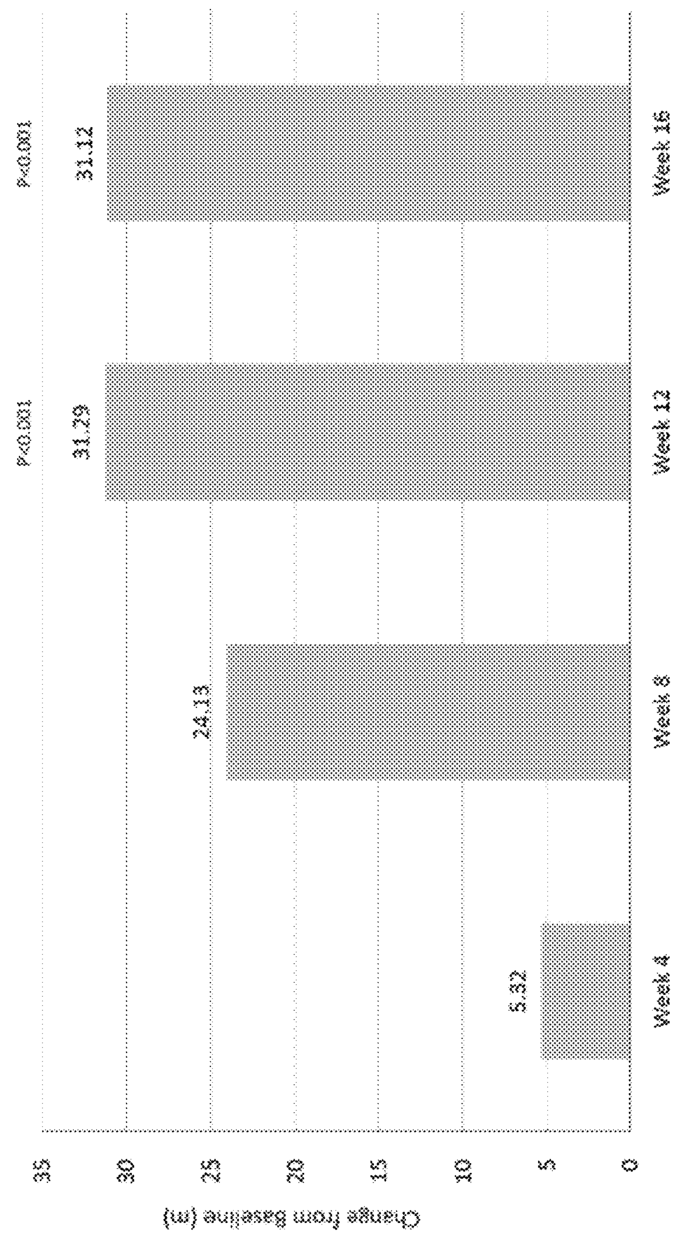

462 Patients were assessed for eligibility
136 Failed screening
326 Underwent randomization
163 Were assigned to receive inhaled treprostinil
163 Were assigned to receive placebo
40 Discontinued treprostinil prematurely
16 Had an adverse event
6 Died
6 Had progressive disease
3 Had protocol violation
7 Withdrew
2 Had other reason
38 Discontinued placebo prematurely
13 Had an adverse event
5 Died
10 Had progressive disease
9 Withdrew
1 Had other reason
33 Discontinued study participation
7 Had an adverse event
8 Died
4 Had progressive disease
2 Had protocol violation
10 Withdrew consent
2 Had other reason
35 Discontinued study participation
3 Had an adverse event
10 Died
1 Was lost to follow-up
7 Had progressive disease
13 Withdrew consent
1 Had other reason
130 Completed week 16 of study assessment
128 Completed week 16 of study assessment

Figure 3



Observed
MMRM
MCMC
Inhaled treprostinil
Placebo
148
132
125
121
148
131
121
120
Change from Baseline (m)
30
25
20
15
10
5
0
-5
-10
-15
-20
Week
0
4
8
12
16

Figure 4



Change from Baseline (m)
0
5
10
15
20
25
30
35
5.32
24.13
31.29
31.12
P<0.001
P<0.001
Week 4
Week 8
Week 12
Week 16

Figure 5

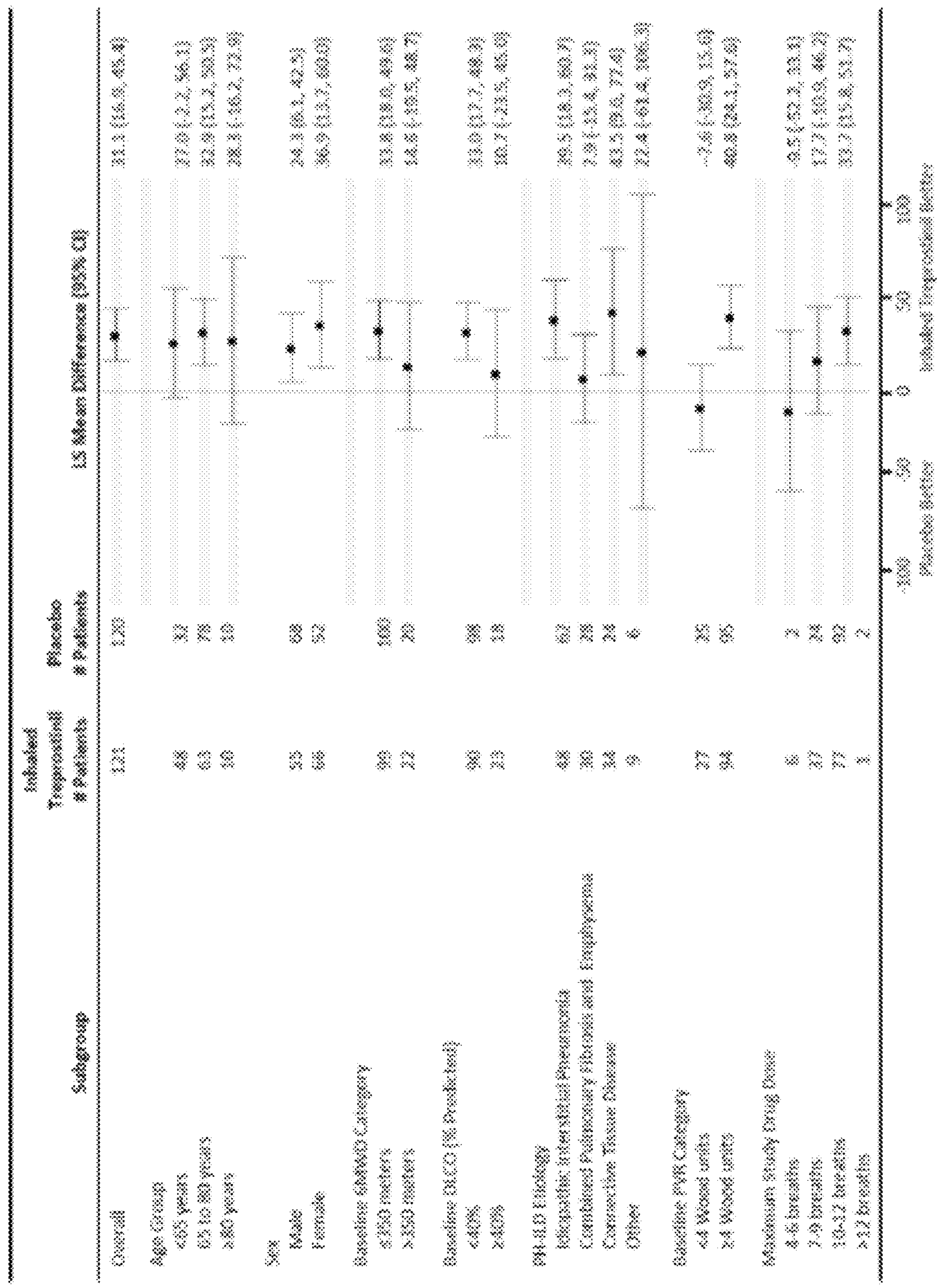

Subgroup
Inhaled Treprostinil # Patients
Placebo # Patients
LS Mean Difference (95% CI)
Overall 121 120 31.1 (16.8, 45.4)
Age Group
<65 years 48 32 27.0 (-2.2, 56.1)
65 to 80 years 63 78 32.9 (15.2, 50.5)
≥80 years 10 10 28.3 (-16.2, 72.9)
Sex
Male 55 68 24.3 (6.1, 42.5)
Female 66 52 36.9 (13.7, 60.0)
Baseline 6MWD Category
≤350 meters 99 100 33.8 (18.0, 49.6)
>350 meters 22 20 14.6 (-19.5, 48.7)
Baseline DLCO (% Predicted)
<40% 98 98 33.0 (17.7, 48.3)
≥40% 23 18 10.7 (-23.5, 45.0)
PH-ILD Etiology
Idiopathic Interstitial Pneumonia 48 62 39.5 (18.3, 60.7)
Combined Pulmonary Fibrosis and Emphysema 30 28 7.9 (-15.4, 31.3)
Connective Tissue Disease 34 24 43.5 (9.6, 77.4)
Other 9 6 22.4 (-61.4, 106.3)
Baseline PVR Category
<4 Wood units 27 25 -7.6 (-30.9, 15.6)
≥4 Wood units 94 95 40.8 (24.1, 57.6)
Maximum Study Drug Dose
4-6 breaths 6 2 -9.5 (-52.2, 33.1)
7-9 breaths 37 24 17.7 (-10.9, 46.2)
10-12 breaths 77 92 33.7 (15.8, 51.7)
>12 breaths 1 2
-100 -50 0 50 100
Placebo Better
Inhaled Treprostinil Better

Figure 6

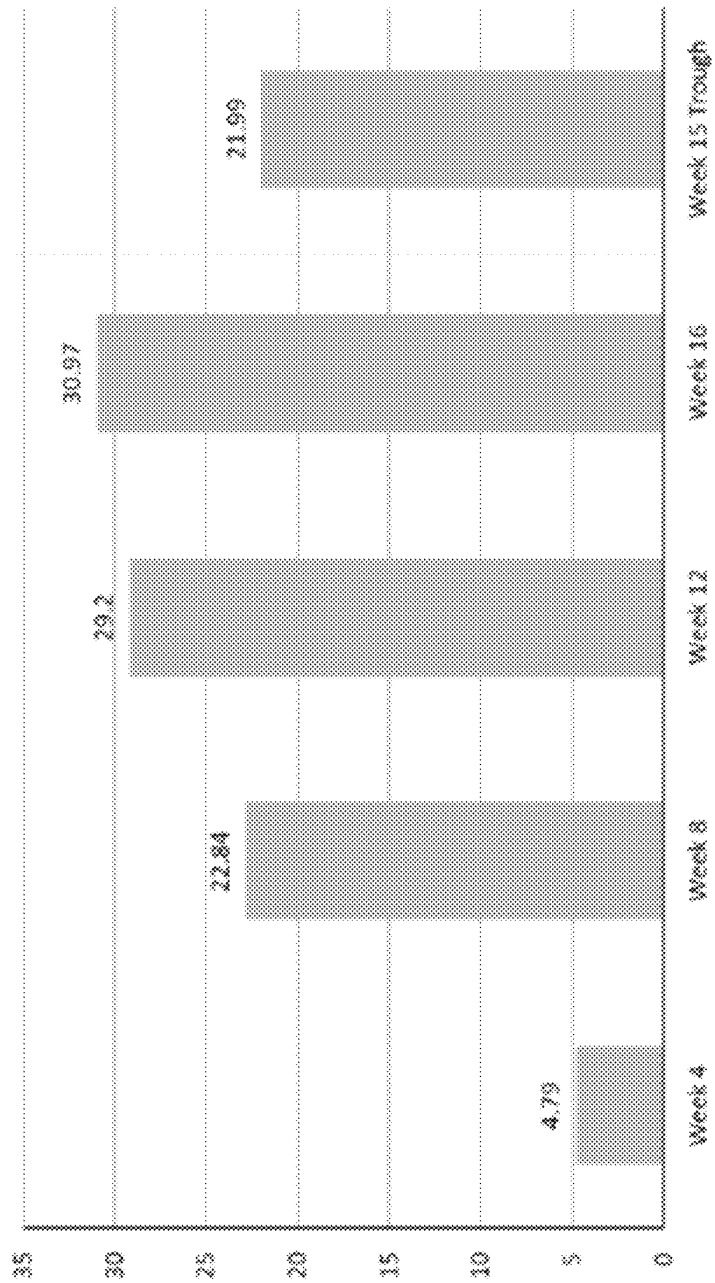

35
30
25
20
15
10
5
0
4.79
22.84
29.2
30.97
21.99
Week 4
Week 8
Week 12
Week 16
Week 15 Trough

Figure 7

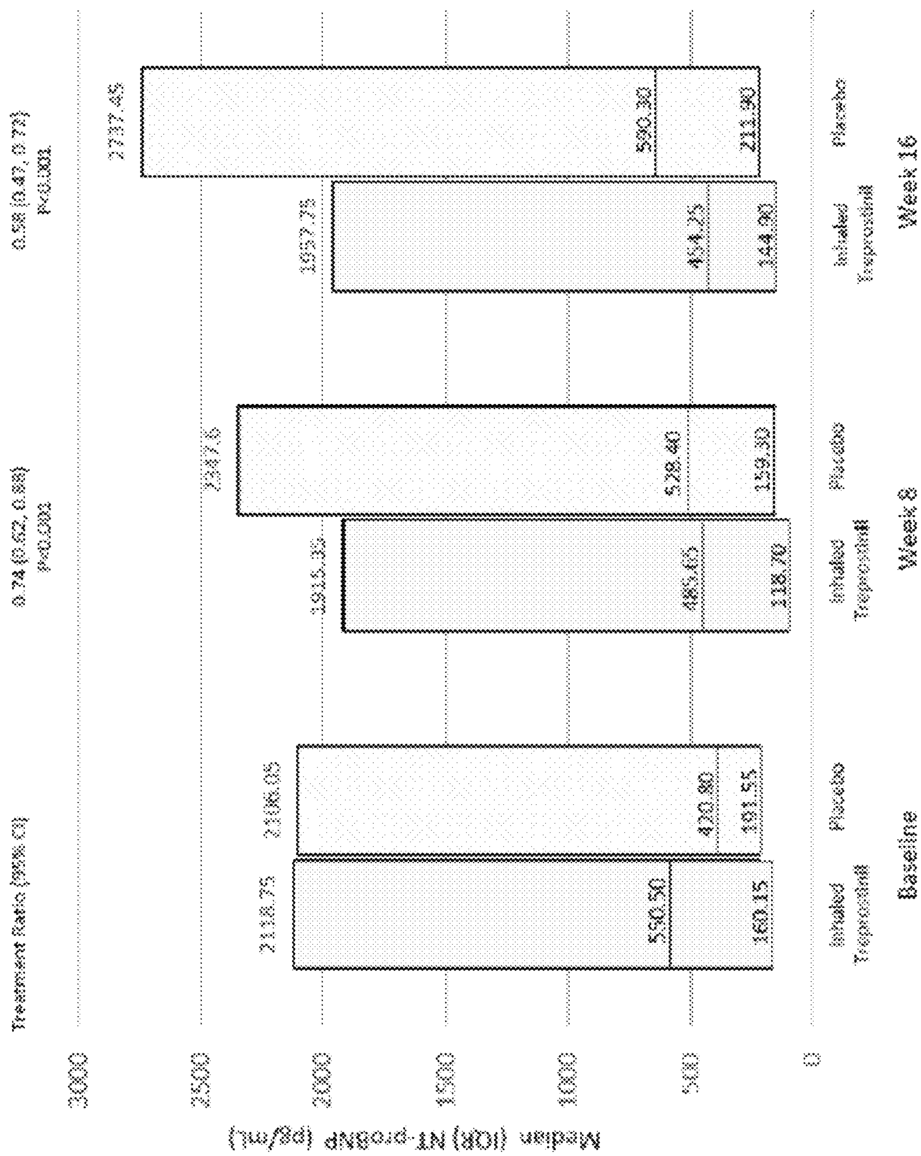

Treatment Ratio (95% CI)
0.74 (0.62, 0.88)
P<0.001
0.58 (0.47, 0.72)
P<0.001
2118.75
550.50
160.15
2106.05
420.90
191.55
1915.35
485.65
118.70
2347.5
528.40
159.30
1957.75
454.25
144.90
2737.45
590.30
211.90
Inhaled Treprostinil
Placebo
Baseline
Week 8
Week 16
Median (IQR) NT-proBNP (pg/mL)
3000
2500
2000
1500
1000
500
0

Figure 8

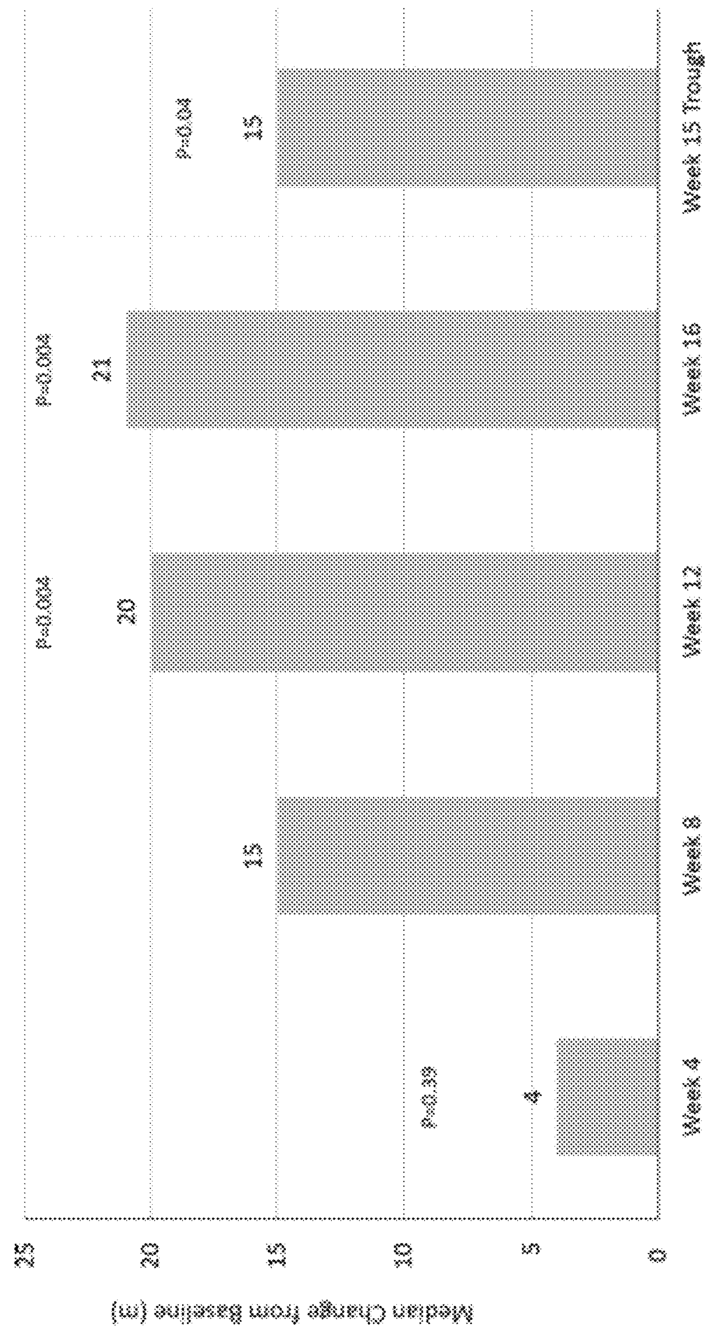

Median Change from Baseline (m)
25
20
15
10
5
0
P=0.39
4
15
P=0.034
20
P=0.034
21
P=0.04
15
Week 4
Week 8
Week 12
Week 16
Week 15 Trough

Figure 9

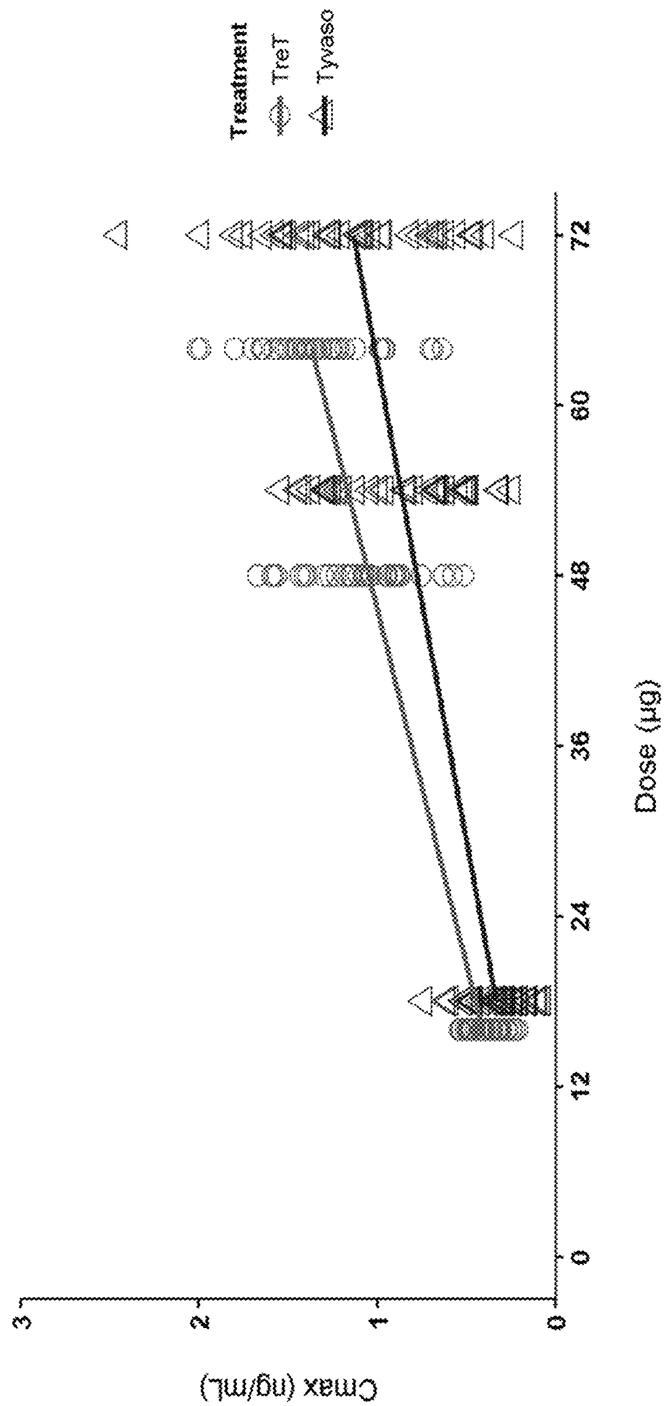

Treatment
TreT
Tyvaso
Cmax (ng/mL)
0
1
2
3
Dose (µg)
0
12
24
36
48
60
72

Figure 10

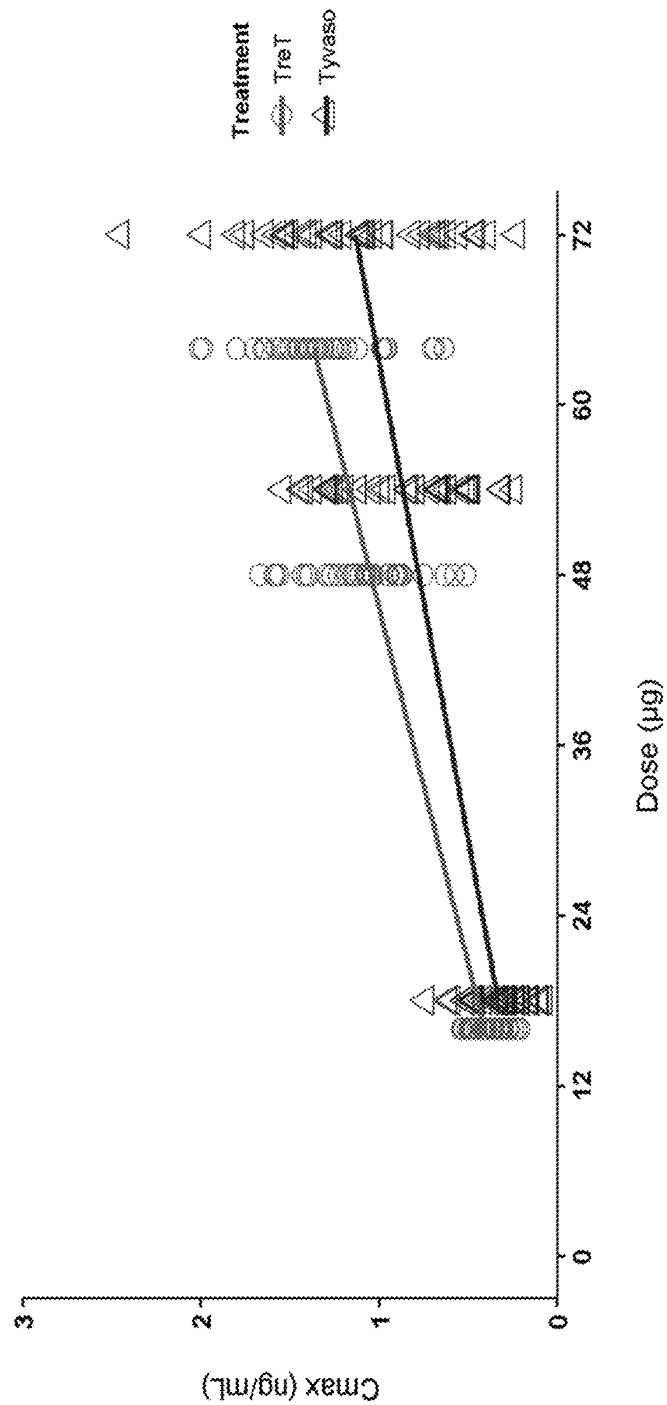
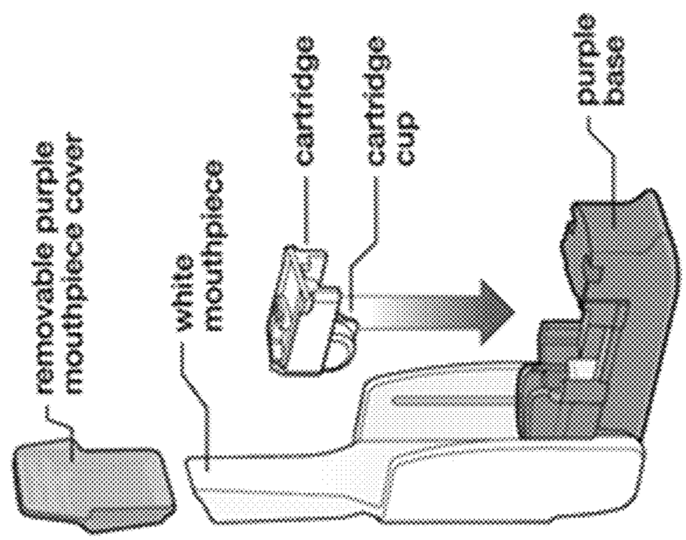

Treatment
TreT
Tyvaso
Cmax (ng/mL)
0
1
2
3
Dose (µg)
0
12
24
36
48
60
72

Figure 11


removable purple mouthpiece cover
white mouthpiece
cartridge
cartridge cup
purple base

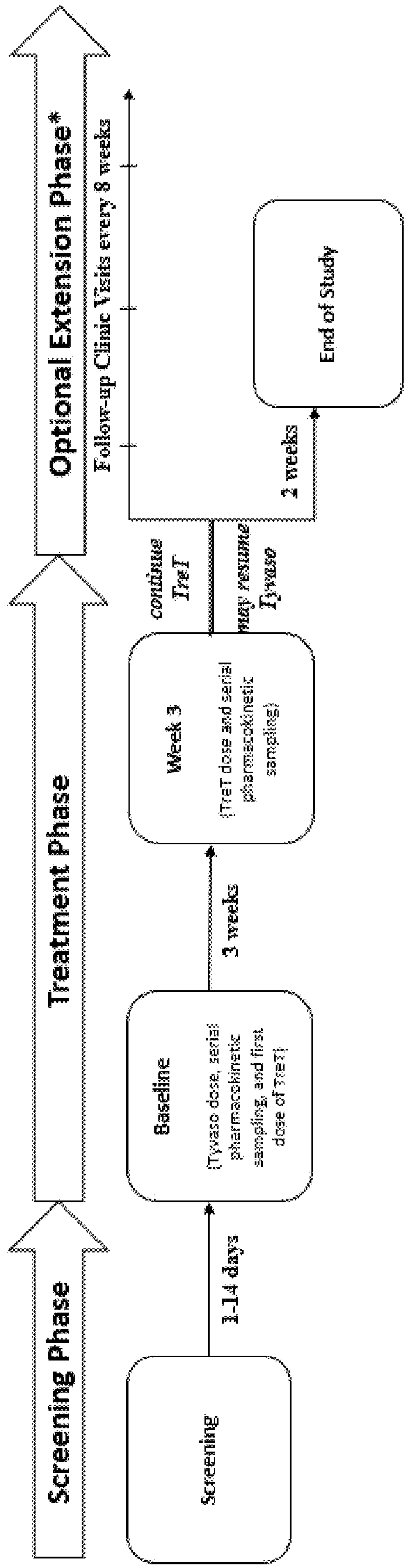

Screening Phase
Treatment Phase
Optional Extension Phase*
Follow-up Clinic Visits every 8 weeks
Screening
1-14 days
Baseline
(Tyvaso dose, serial pharmacokinetic sampling, and first dose of TreT)
3 weeks
Week 3
(TreT dose and serial pharmacokinetic sampling)
continue TreT
may resume Tyvaso
2 weeks
End of Study

Figure 12

Figure 13

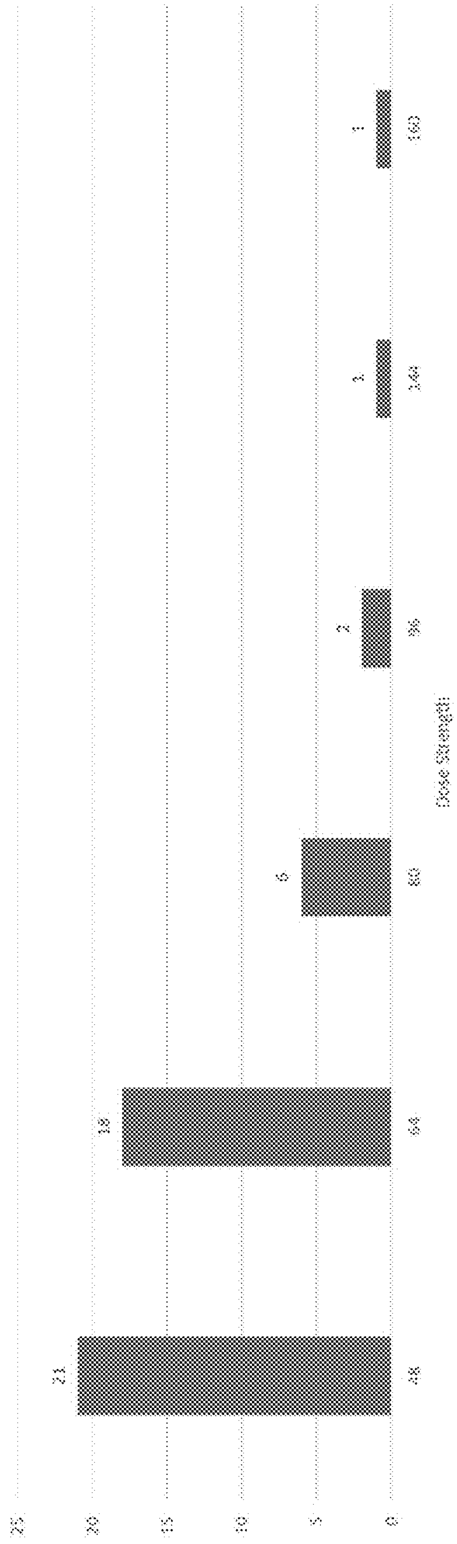


Figure 14

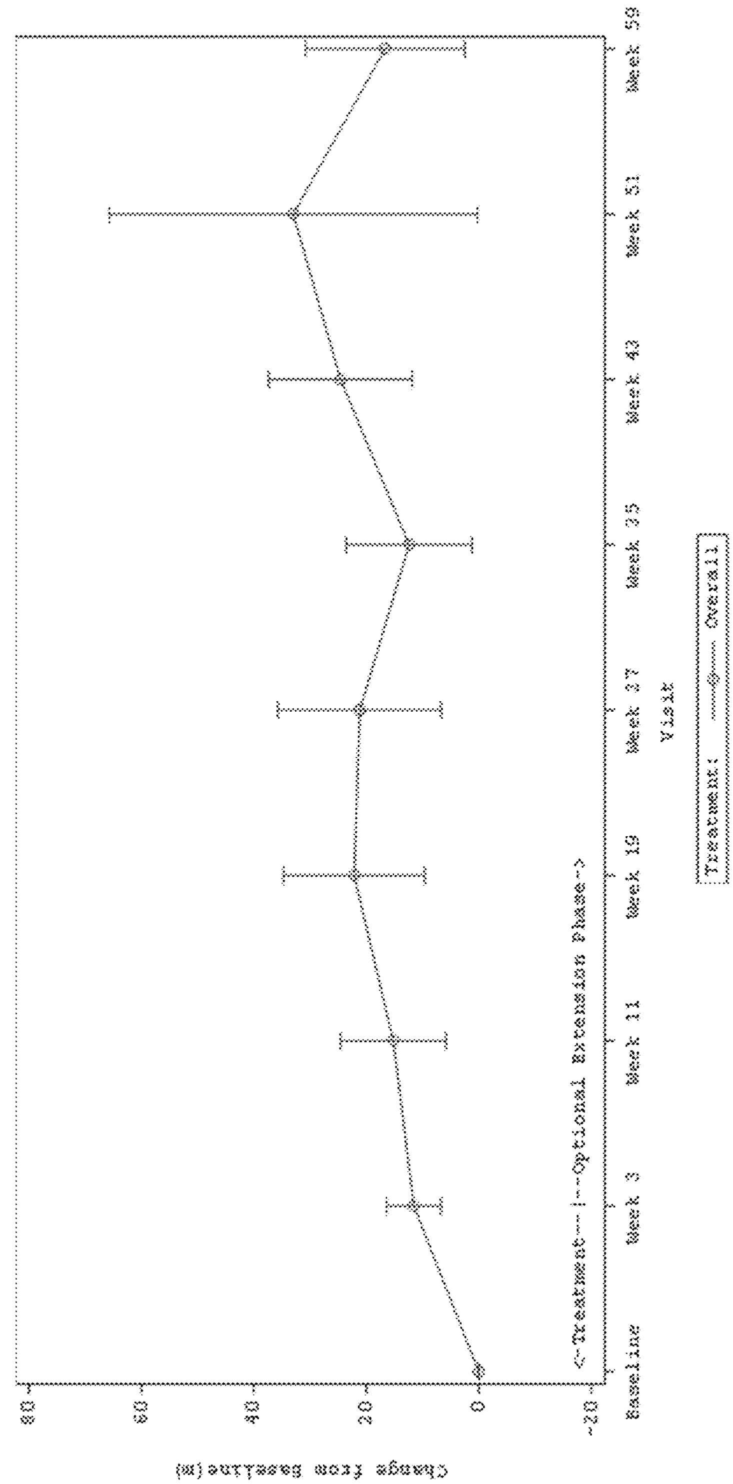
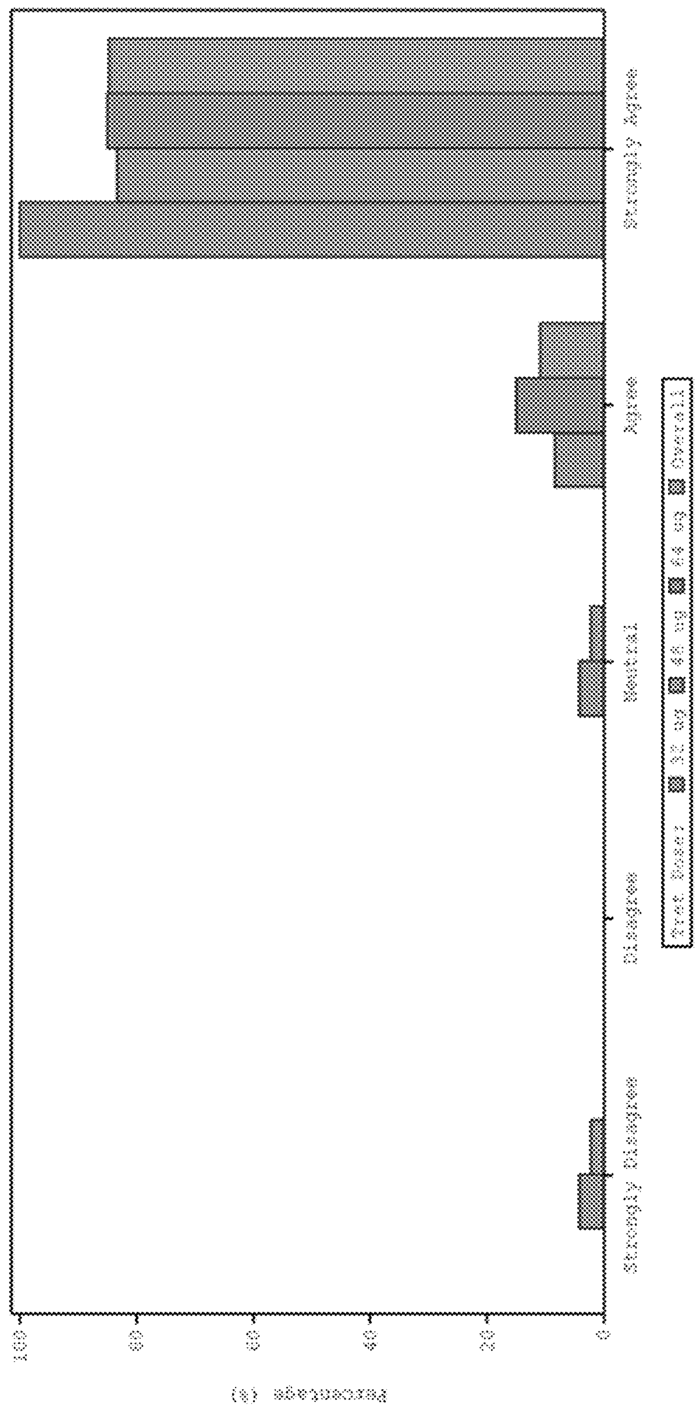

Change from baseline(m)
80
60
40
20
0
-20
Baseline
Week 3
Week 11
Week 19
Week 27
Week 35
Week 43
Week 51
Week 59
Visit
<--Treatment---|--Optional Extension Phase-->
Treatment: Overall

Figure 15


Strongly Agree
Agree
Neutral
Disagree
Strongly Disagree
Percentage (%)
0
20
40
60
80
100

TREATMENT FOR INTERSTITIAL LUNG DISEASE

RELATED APPLICATIONS

The present application claims priority to U.S. provisional application No. 63/011,810 filed Apr. 17, 2020 and U.S. provisional application No. 63/160,611 filed Mar. 12, 2021, each of which is incorporated herein by reference in its entirety.

FIELD

The present application generally relates to methods of treating a disease with prostacyclins and more particularly, to treating a disease with treprostinil.

BACKGROUND

Interstitial lung disease (ILD), or diffuse parenchymal lung disease (DPLD), is a group of lung diseases affecting the interstitium (the tissue and space around the alveoli, including air sacs of the lungs). It concerns alveolar epithelium, pulmonary capillary endothelium, basement membrane, and perivascular and perilymphatic tissues. It may occur when an injury to the lungs triggers an abnormal healing response. Such abnormal response may result in idiopathic pulmonary fibrosis (IPF). Currently, two drugs are approved by FDA for treatment of IPF, which is the most common form of PF: nintedanib and pirfenidone. The average rate of survival for someone with interstitial lung disease is currently between 3 and 5 years (Meyer et al., 2017). There exists a need for the identification of new pharmaceutical treatments for ILD.

SUMMARY

In one aspect, a method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprises administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.

In one aspect, a method of treating interstitial lung disease (ILD) in a subject in need thereof is provided, comprises administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof. In an embodiment, the subject has pulmonary hypertension associated with ILD.

In one aspect, a method of reducing pulmonary function decline in a subject with ILD is provided, comprises administering to the subject treprostinil, a prodrug, salt, or ester thereof.

In one aspect, a method of increasing forced vital capacity (FVC) in a subject suffering from ILD is provided, comprises administering to the subject treprostinil, a prodrug, salt, or ester thereof. In some embodiments, administration of treprostinil, a prodrug, salt, or ester thereof may result in an increase of FVC of at least 20%, at least 40%, at least 60%, at least 80%, at least 90%, or at least 100% compared to the FVC prior to the start of treatment. The FVC can be assessed prior to the start of treatment and at intervals after the start of treatment. For example, the pre-treatment FVC can be compared to the FVC measured at one week, four weeks, eight weeks, or sixteen weeks after the start of treatment.

In some embodiments, administering an effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an improvement, which may be statistically significant, in forced vital capacity (FVC) in a subject with a condition selected from a chronic lung disease, such as an ILD or IPF and/or hypoxia. For example, the FVC may be higher in a patient subpopulation with the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks, or at least 28 weeks or at least 32 weeks, or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the FVC value may be higher by at least 10 ml or at least 15 ml or at least 20 ml or at least 25 ml or at least 30 ml or at least 35 ml or at least 40 ml or at least 45 ml after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering in the patient subpopulation with the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug compared to the patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. In patients with a chronic lung disease, such as interstitial lung disease, and/or hypoxia, an FVC value usually decreases with time when untreated. Thus, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt may increase an FVC value compared to an FVC value before the administering; maintain an FVC value within 5%, 10% or 20% within the FVC value prior to the administering; or reduce a decrease of an FVC value with time compared to a decrease in an FVC value with no administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt, such a decrease in an FVC value when placebo is administered instead of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt.

In some embodiments, the ILD comprises one or more of idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhan's cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis. In some embodiments, the ILD comprises IPF.

In some embodiments, the ILD comprises systemic sclerosis-associated interstitial lung disease (SSc-ILD).

In some embodiments, the ILD was induced from antibiotics, chemotherapy, antiarrhythmic agents, coronavirus disease 2019 (COVID-19), atypical pneumonia, pneumocystis pneumonia, tuberculosis (TB), *Chlamydia trachomatis*, respiratory syncytial virus, or lymphangitic carcinomatosis.

In some embodiments, the subject has one or more of surfactant-protein-B deficiency, surfactant-protein-C deficiency, ABCA3-deficiency, brain lung thyroid syndrome, congenital pulmonary alveolar proteinosis, alveolar capillary dysplasia, mutations in telomerase reverse transcriptase, mutations in telomerase RNA component, mutations in the regulator of telomere elongation helicase 1, and mutations in poly(A)-specific ribonuclease.

In some embodiments, the subject has one or more symptoms of shortness of breath, fatigue, weight loss, dry cough, chest pain, and lung hemorrhage. In some embodiments, after administration the symptom is improved by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as measured by a medically-recognized technique. In some embodiments, the medically-recognized technique comprises one or more of Modified Medical Research Council (MMRC) Dyspnoea Scale, Modified Borg Dyspnoea Scale (0-10), Chalder Fatigue Scale, weight measurement scale, visual analogue scale (VAS) for cough, King's Brief Interstitial Lung Disease Questionnaire, Leicester Cough Questionnaire (LCQ), Living with IPF (L-IPF, see e.g. Am J Respir Crit Care Med Vol 202, Iss 12, pp 1689-1697, Dec. 15, 2020), computed tomography (CT) scan, X-ray, multiple magnetic resonance imaging (MRI), pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

In some embodiments, treprostinil, a prodrug, salt, or ester thereof is administered in a pharmaceutical composition comprising treprostinil, a prodrug, salt, or ester thereof and a pharmaceutically acceptable carrier or excipient.

In some embodiments, the administration comprises at least one of oral, inhalation, subcutaneous, nasal, intravenous, intramuscular, sublingual, buccal, rectal, vaginal, and transdermal administration. In some embodiments, the administration comprises inhalation. In some embodiments, one inhalation dosing event comprises from 1 to 20 breaths, wherein at least one inhalation dosing event per day is administered.

In some embodiments, the method comprises administration of at least one additional active agent to treat the ILD. In some embodiments, the at least one additional active agent comprises a corticosteroid, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, pirfenidone, or nintedanib. In some embodiments, the at least one additional active agent and treprostinil, a prodrug, salt, or ester thereof, are administered via a method selected from the group consisting of (a) concomitantly; (b) as an admixture; (c) separately and simultaneously or concurrently; and (d) separately and sequentially.

In some embodiments, administration is once, twice, thrice, four times, five times, or six times per day. In some embodiments, administration is for a period selected from the group consisting of about 1 day, about 1 day to about 3 days, about 3 days to about 6 days, about 6 days to about 9 days, about 9 days to about 12 days, about 12 days to about 15 days, about 15 days to about 18 days, about 18 days to about 21 days, about 21 days to about 24 days, about 24 days to about 27 days, about 27 days to about 30 days, or about greater than 30 days.

In some embodiments, a method of treating a pulmonary hypertension due to a condition which is selected from a chronic lung disease, hypoxia and a combination thereof, comprises administering to a subject having the pulmonary hypertension due to the condition selected from a chronic lung disease, hypoxia and a combination thereof an effective amount of treprostinil, a prodrug thereof or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject is a human.

FIGURES

FIG. **1** shows a Kaplan-Meier plot of time to exacerbation of underlying lung disease over a 16-week period of treprostinil treatment. CI stands for confidence interval; HR stands for hazard ratio. Subjects who discontinued from the study early had their time to first clinical worsening event censored at their last visit. Subjects who did not experience a clinical worsening event had their time to first clinical worsening event censored at the study termination date. (1) P-value was calculated with log-rank test stratified by baseline 6-minute walk distance category. (2) Hazard ratio, 95% CI, and p-value were calculated with proportional hazards model with treatment and baseline 6-minute walk distance (continuous) as explanatory variables.

FIG. **2** outlines a plan for the clinical study presented in Example 3. Of 462 patients screened for eligibility, 326 patients underwent randomization and received at least one dose of the assigned treprostinil or placebo (included in the intention-to-treat and safety populations). Of the patients who underwent randomization, 40 patients in the treprostinil group and 38 in the placebo group discontinued the assigned regimen prematurely. These patients were not withdrawn from the trial but were encouraged to remain and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued trial participation before week 16.

FIG. **3** shows mean change from baseline in peak 6-minute walking distance through week 16 in the clinical study presented in Example 3. Shown are mean (±SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

FIG. **4** shows 6-Minute Walk Distance Treatment Effect Using Mixed Model Repeated Measurement Through Week 16. A longitudinal data analysis using mixed model repeated

measurement was also performed to estimate the treatment difference in change in peak 6-minute walk distance at Week 16. The mixed model repeated measurement includes the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment by week interaction as fixed effects; and baseline 6-minute walk distance as a covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

FIG. **5** shows Forest Plot on Subgroup Analyses of Peak 6-Minute Walk Distance (meter) at Week 16. 6MWD stands for 6-minute walk distance; CI stands for confidence interval; ILD stands for interstitial lung disease; PH stands for pulmonary hypertension; PVR stands for pulmonary vascular resistance; LS mean differences and their 95% confidence intervals, and p-values are from the mixed model repeated measures. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. For etiology, the “other” category includes chronic hypersensitivity pneumonitis and occupational lung disease.

FIG. **6** shows 6-Minute Walk Distance Treatment Effect Using Multiple Imputation Through Week 16. Multiple imputation approach using a multivariate normal imputation model with the Markov Chain Monte Carlo method. P-values are obtained from 100 multiple imputations using Markov Chain Monte Carlo estimation with ANCOVA model with change from Baseline in 6-minute walk distance as the dependent variable, treatment as fixed effect, and Baseline 6-minute walk distance measurement as a covariate.

FIG. **7** shows NT-proBNP Results by Study Visit (pg/mL). CI stands for confidence interval; IQR stands for interquartile range; NT-proBNP stands for N-terminal pro-brain natriuretic peptide. As displayed above, inhaled treprostinil was associated with a 42% reduction in NT-proBNP compared to placebo at Week 16 (Treatment Ratio 0.58; 95% CI: 0.47, 0.72; P<0.001). Only subjects with a Baseline NT-proBNP measurement are included in this analysis. P-values, estimated treatment ratio, and associated 95% CIs (LS Mean difference expressed as ratio) are obtained from the analysis of covariance with change from baseline in log transformed data in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

FIG. **8** shows Hodges-Lehmann Estimate of Treatment Effect for 6-Minute Walk Distance Through Week 16. For those subjects who withdrew early due to death, were too ill to walk, or had no 6-minute walk distance measurement due to a clinical worsening event, the 6-minute walk distance was set to 0; for all other withdrawals without a measurement, last observation carried forward was used for imputation. P-values are obtained from nonparametric ANCOVA adjusted for Baseline 6-minute walk distance category.

FIG. **9** is a plot showing a relationship between treprostinil AUC0-5 and dose for Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler and nebulized treprostinil administered by Tyvaso nebulizer.

FIG. **10** is a plot showing a relationship between treprostinil Cmax and dose for Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler and nebulized treprostinil administered by Tyvaso nebulizer.

FIG. **11** shows a dry powder inhaler, which has a cartridge with a dose of Treprostinil Inhalation Powder (TreT).

FIG. **12** shows a design of a study of Example 5. During the Optional Extension Phase (OEP), dosing titration is encouraged; the dose of TreT is titrated upward, as clinically tolerated, to identify a maximum stable dose in each subject.

FIG. **13** shows a number of subjects for various maintenance TreT doses in the OEP.

FIG. **14** shows a change in 6 minute walk distance (6MWD) with respect to a baseline 6MWD as a function of duration of TreT treatment.

FIG. **15** is a plot reporting satisfaction of participants of the study of Example 5.

DETAILED DESCRIPTION

It is noted that, as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements or use of a “negative” limitation.

As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, but do not exclude others. A composition or method “consisting essentially” of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed technology. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this technology. When an embodiment is defined by one of these terms (e.g., “comprising”) it should be understood that this disclosure also includes alternative embodiments, such as “consisting essentially of” and “consisting of” for said embodiment.

“Subject” refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. “Subject” and “patient” may be used interchangeably, unless otherwise indicated. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

The terms “therapeutically effective amount,” “effective amount,” and “pharmaceutically effective amount” are used interchangeably and refer to an amount of a compound that is sufficient to effect treatment as defined below, when administered to a patient (e.g., a human) in need of such treatment in one or more doses. The therapeutically effective amount will vary depending upon the patient, the disease being treated, the weight and/or age of the patient, the severity of the disease, or the manner of administration as determined by a qualified prescriber or care giver. The therapeutically effective amount can be determined by titrating the dose upwards from a starting dose, either in terms of dose by administration or frequency of administration. In some embodiments, the therapeutically effective dose is determined by titrating the dose upwards until the maximum tolerated dose for the individual subject is determined.

The term “treatment” or “treating” means administering a compound disclosed herein for the purpose of (i) delaying the onset of a disease, that is, causing the clinical symptoms of the disease not to develop or delaying the development thereof, (ii) inhibiting the disease, that is, arresting the

development of clinical symptoms; and/or (iii) relieving the disease, that is, causing the regression of clinical symptoms or the severity thereof.

The term "pulmonary fibrosis" is a condition characterized by scarring and thickening of the lungs. Symptoms include shortness of breath, fatigue, weakness, chronic dry, hacking cough, loss of appetite, and discomfort in the chest. Eventually the scarring in the lung becomes replaced with fibrotic tissue resulting in loss of the lung's ability to transfer oxygen to the blood.

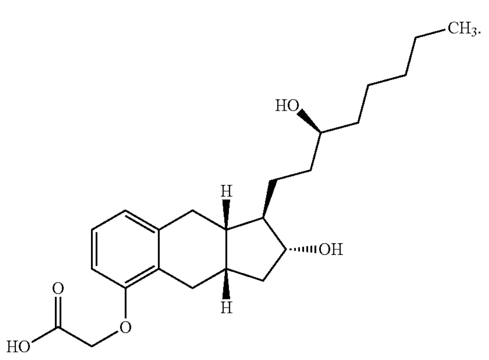
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this present technology belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present technology, representative illustrative methods and materials are described herein.

All numerical designations, e.g., pH, temperature, time, concentration, dose, and molecular weight, including ranges, are approximations which are varied (+) or (−) by increments of 0.05%, 1%, 2%, 5%, 10% or 20%. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term "about."

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the present technology. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the present technology, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the present technology.

In an aspect, the present disclosure provides a method of treating interstitial lung disease (ILD) in a subject in need, comprising administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof.

Treprostinil is used for the treatment of pulmonary arterial hypertension. Treprostinil is a synthetic analog of prostacyclin (PGI_2) having the structure:



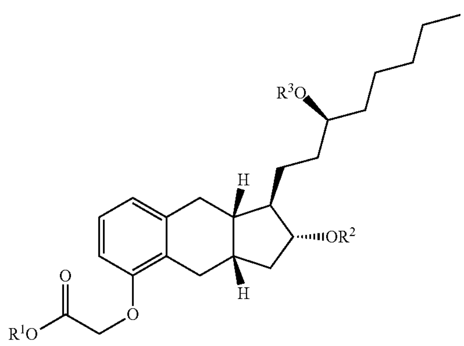
Treprostinil, the active ingredient in Remodulin® (treprostinil) Injection, Tyvaso® (treprostinil) Inhalation Solution, and Orenitram® (treprostinil) Extended Release Tablets, was described in U.S. Pat. No. 4,306,075. Methods of making treprostinil and other prostacyclin derivatives are described, for example, in Moriarty, et al., J. Org. Chem. 2004, 69, 1890-1902, Drug of the Future, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,700,025, 6,809,223, 6,756,117, 8,461,393, 8,481,782; 8,242,305, 8,497,393, 8,940,930, 9,029,607, 9,156,786 and 9,388,154 9,346,738; U.S. Published Patent Applications Nos. 2012-0197041, 2013-0331593, 2014-0024856, 2015-0299091, 2015-0376106, 2016-0107973, 2015-0315114, 2016-0152548, and 2016-0175319; PCT Publications No. WO2016/0055819 and WO2016/081658.

Various uses and/or various forms of treprostinil are disclosed, for example, in U.S. Pat. Nos. 5,153,222, 5,234,953, 6,521,212, 6,756,033, 6,803,386, 7,199,157, 6,054,486, 7,417,070, 7,384,978, 7,879,909, 8,563,614, 8,252,839, 8,536,363, 8,410,169, 8,232,316, 8,609,728, 8,350,079, 8,349,892, 7,999,007, 8,658,694, 8,653,137, 9,029,607, 8,765,813, 9,050,311, 9,199,908, 9,278,901, 8,747,897, 9,358,240, 9,339,507, 9,255,064, 9,278,902, 9,278,903, 9,758,465; 9,422,223; 9,878,972; 9,624,156; U.S. Published Patent Applications Nos. 2009-0036465, 2008-0200449, 2008-0280986, 2009-0124697, 2014-0275616, 2014-0275262, 2013-0184295, 2014-0323567, 2016-0030371, 2016-0051505, 2016-0030355, 2016-0143868, 2015-0328232, 2015-0148414, 2016-0045470, 2016-0129087, 2017-0095432; 2018-0153847 and PCT Publications Nos. WO00/57701, WO20160105538, WO2016038532, WO2018/058124.

A "prodrug" of treprostinil may refer to compounds which are converted in vivo to treprostinil or its pharmaceutically active derivatives thereof, or to a compound described in PCT publication No. WO2005/007081; U.S. Pat. Nos. 7,384,978, 7,417,070, 7,544,713, 8,252,839, 8,410,169, 8,536,363, 9,050,311, 9,199,908, 9,278,901, 9,422,223; 9,624,156, 9,878,972, 9,371,264, 9,394,227, 9,505,737, 9,758,465, 9,643,911, 9,701,616, 9,776,982, 9,845,305, 9,957,200, 10,494,327, 10,053,414, 10,246,403, 10,344,012, 10,450,290, 10,464,877, 10,464,878, 10,703,706, 10,752,733, 9,255,064, 9,469,600, 10,010,518, 10,343,979, 10,526,274; U.S. Patent Application Publications Nos. 2018-0153847 and 2021-0054009; U.S. provisional patent application No. 63/036,561 filed Jun. 9, 2020; U.S. provisional patent application No. 63/125,145 filed Dec. 14, 2020, each of which is incorporated herein by reference in their entirety.

Prostacyclin is a small molecule that has been previously shown to cause dilation of large blood vessels, relaxation of smooth muscle, inhibition of smooth muscle proliferation, as well as inhibition of platelet aggregation, which is involved in the blood clotting process. Similar actions by treprostinil at the microvascular level and on capillaries near the skin are believed to help enhance cutaneous blood flow and heal and/or prevent ischemia lesions or ulcers associated with scleroderma, Buerger's disease, Raynaud's disease, Raynaud's phenomenon, and other conditions.

An "ester" of treprostinil may refer to a compound of formula:



wherein

R^1 is H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

R^2 and R^3 are each independently —C(O)R^4; and

each R^4 is independently optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclyl;

wherein at least one of R^1, R^2, and R^3, is not H.

"Optionally substituted" refers to a group selected from that group and a substituted form of that group. Substituents may include any of the groups defined below. In one embodiment, substituents are selected from C_1-C_{10} or C_1-C_6 alkyl, substituted C_1-C_{10} or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_5 cycloalkyl, C_2-C_{10} heterocyclyl, C_1-C_{10} heteroaryl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, substituted C_6-C_{10} aryl, substituted C_3-C_8 cycloalkyl, substituted C_2-C_{10} heterocyclyl, substituted C_1-C_{10} heteroaryl, halo, nitro, cyano, —CO_2H or a C_1-C_6 alkyl ester thereof.

"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3—), ethyl (CH_3CH_2—), n-propyl ($CH_3CH_2CH_2$—), isopropyl ($(CH_3)_2CH$—), n-butyl ($CH_3CH_2CH_2CH_2$—), isobutyl ($(CH_3)_2CHCH_2$—), sec-butyl ($(CH_3)(CH_3CH_2)CH$—), t-butyl ($(CH_3)_3C$—), n-pentyl ($CH_3CH_2CH_2CH_2CH_2$), and neopentyl ($(CH_3)_3CCH_2$—).

"Alkenyl" refers to monovalent straight or branched hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl (>C═C<) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but 3-en-1-yl. Included within this term are the cis and trans isomers or mixtures of these isomers.

"Alkynyl" refers to straight or branched monovalent hydrocarbyl groups having from 2 to 10 carbon atoms and preferably 2 to 6 carbon atoms or preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic (—C≡C—) unsaturation. Examples of such alkynyl groups include acetylenyl (—C≡CH), and propargyl (—CH_2C≡CH).

"Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester) amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxyl, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester) amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, sub-

stituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, substituted sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are as defined herein and with the proviso that any hydroxyl or thiol substitution is not attached to an acetylenic carbon atom.

"Alkoxy" refers to the group 0 alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n propoxy, isopropoxy, n butoxy, t butoxy, sec butoxy, and n pentoxy.

"Substituted alkoxy" refers to the group 0 (substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H—C(O)—, alkyl-C(O)—, substituted alkyl-C(O)—, alkenyl-C(O)—, substituted alkenyl-C(O)—, alkynyl-C(O)—, substituted alkynyl-C(O)—, cycloalkyl-C(O)—, substituted cycloalkyl-C(O)—, cycloalkenyl-C(O)—, substituted cycloalkenyl-C(O)—, aryl-C(O)—, substituted aryl-C(O)—, heteroaryl-C(O)—, substituted heteroaryl-C(O)—, heterocyclic-C(O)—, and substituted heterocyclic-C(O)—, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$—.

"Acylamino" refers to the groups —NR^{47}C(O)alkyl, —NR^{47}C(O)substituted alkyl, —NR^{47}C(O)cycloalkyl, —NR^{47}C(O)substituted cycloalkyl, —NR^{47}C(O)cycloalkenyl, —NR^{47}C(O)substituted cycloalkenyl, —NR^{47}C(O) alkenyl, —NR^{47}C(O)substituted alkenyl, —NR^{47}C(O)alkynyl, —NR^{47}C(O)substituted alkynyl, —NR^{47}C(O)aryl, —NR^{47}C(O)substituted aryl, —NR^{47}C(O)heteroaryl, —NR^{47}C(O)substituted heteroaryl, —NR^{47}C(O)heterocyclic, and NR^{47}C(O)substituted heterocyclic wherein R^{47} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O—, substituted alkyl-C(O)O—, alkenyl-C(O)O—, substituted alkenyl-C(O)O—, alkynyl-C(O)O—, substituted alkynyl-C(O)O—, aryl-C(O)O—, substituted aryl-C(O)O—, cycloalkyl-C(O)O—, substituted cycloalkyl-C(O)O—, cycloalkenyl-C(O)O—, substituted cycloalkenyl-C(O)O—, heteroaryl-C(O)O—, substituted heteroaryl —C(O)O, heterocyclic-C(O)O—, and substituted heterocyclic-C(O)O— wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Amino" refers to the group NH_2.

"Substituted amino" refers to the group —$NR^{48}R^{49}$ where R^{48} and R^{49} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, SO_2 alkyl, —SO_2-substituted alkyl, —SO_2-alkenyl, —SO_2-substituted alkenyl, —SO_2-cycloalkyl, —SO_2-substituted cycloalkyl, —SO_2-cycloalkenyl, —SO_2-substituted cylcoalkenyl, —SO_2-aryl, —SO_2-substituted aryl, —SO_2-heteroaryl, —SO_2-substituted heteroaryl, —SO_2-heterocyclic, and —SO_2-substituted heterocyclic and wherein R^{48} and R^{49} are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R^{48} and R^{49} are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. When R^{48} is hydrogen and R^{49} is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R^{48} and R^{49} are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino.

When referring to a monosubstituted amino, it is meant that either R^{48} or R^{49} is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^{48} nor R^{49} are hydrogen.

"Pharmaceutically acceptable salt" may refer to physiologically acceptable salts of treprostinil, as well as non-physiologically acceptable salts of treprostinil. Pharmaceutically acceptable salts of compounds described herein are within the scope of the present technology and include acid or base addition salts which retain the desired pharmacological activity and is not biologically undesirable (e.g., the salt is not unduly toxic, allergenic, or irritating, and is bioavailable). When the compound of the present technology has a basic group, such as, for example, an amino group, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid), organic acids (e.g., alginate, formic acid, acetic acid, benzoic acid, gluconic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, naphthalene sulfonic acid, and p toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). When the compound of the present technology (treprostinil, an ester, prodrug, or derivative thereof) has an acidic group, such as for example, a carboxylic acid group, it can form salts with metals, such as alkali and earth alkali metals (e.g., Na^+, Li^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}), ammonia or organic amines (e.g., dicyclohexylamine, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine) or basic amino acids (e.g., arginine, lysine and ornithine). Such salts can be prepared in situ during isolation and purification of the compounds or by separately reacting the purified compound in its free base or free acid form with a suitable acid or base, respectively, and isolating the salt thus formed.

ILD may include a range of diseases and disorders, for example, idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis.

"Pulmonary function" as used herein, refers to the ability of the lungs to absorb oxygen and expand and contract. Pulmonary function, decline thereof, or reduction of the decline, may be assessed using medically recognized tools known to those having ordinary skill in the art. Methods

include pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

"Forced vital capacity" as used herein, refers to the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible, as measured by spirometry.

Further aspects of the present invention are concerned with the use of treprostinil or its derivatives, prodrugs, esters, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment or prevention of interstitial lung disease or a condition associated with interstitial lung disease. In some embodiments, the medicament is formulated for inhalation. When administered by inhalation, the formulation can be nebulized or formulated for a dry powder inhaler (DPI).

The amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, that is required in methods may depend on a number of factors, such as the specific indication it is being used for, the nature of the particular compound used, the mode of administration, the concentration, and the weight and condition of the subject. A daily dose per subject for ILD, or conditions associated with ILD may be in the range 25 μg to 250 mg or 7 μg to 285 μg, per day per kilogram bodyweight. In some embodiments, the daily dose may be in the range of about 150 μg to about 350 μg per day, about 200 μg to about 300 μg per day, or about 225 μg to about 275 μg per day. Intravenous doses in the range 0.5 μg to 1.5 mg per kilogram bodyweight per day may be administered as an infusion of from 0.5 ng to 1.0 μg per kilogram bodyweight per minute.

The treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, can be administered using any suitable treatment schedule. In some embodiments, the drug will be administered multiple times a day (1, 2, 3, 4, or 5), and in other embodiments, the drug can be continuously administered, such as by using an infusion pump. The duration of treatment can vary depending on the severity of disease, treatment goals, or individual circumstances. In some embodiments, the duration of treatment is at least one week, at least two weeks, at least four weeks, at least eight weeks, or at least sixteen weeks. In some embodiments, the duration of treatment is indefinite, e.g., treatment can continue for the life of the subject or until disease symptoms decrease below some threshold.

Pharmaceutical compositions described herein or administered to subjects, hereinafter referred to as a "formulation" or "composition," of treprostinil and/or its prodrugs, esters, derivatives, and/or pharmaceutically acceptable salts thereof, may be admixed with, inter alia, an acceptable carrier. The carrier may be compatible with any other ingredients in the formulation and not deleterious to the subject. The carrier may be a solid or a liquid, or both. One or more of treprostinil or its derivatives, esters, prodrugs, or pharmaceutically acceptable salts thereof, may be incorporated in the formulations of the invention. Formulations administered include those suitable for parenteral, oral, inhalation, rectal, topical, buccal and transdermal administration.

Parenterally administered compositions may be isotonic with the blood of the intended recipient. Subcutaneous injection, intravenous, intramuscular or intradermal injection may be used. Such preparations may conveniently be prepared by admixing the compound with water or a glycine or citrate buffer and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for oral administration may be presented as capsules, cachets, lozenges, or tablets, each containing a specific amount of treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Oral formulations that may be administered include those described in U.S. Pat. Nos. 7,384,978 and 8,747,897 (including the commercial product Orenitram® (treprostinil) Extended-Release Tablets), the entire disclosures of which are hereby incorporated by reference. In general, the formulations of the invention are prepared by uniformly and intimately admixing treprostinil, an ester, prodrug, or salt thereof with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, with one or more solid carriers.

Topical and transdermal formulations me be an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers possible include vaseline, lanoline, polyethylene glycols, alcohols, and combinations thereof.

Treprostinil, prodrugs, esters, and salts thereof are conveniently prepared by methods the same as or analogous to those described in U.S. Pat. Nos. 4,306,075, 6,528,688 and 6,441,245, the disclosures of which are hereby incorporated by reference.

In some embodiments of the present methods, the treprostinil administered is provided as a kit with instructions for use in treating ILD. In certain kit embodiments, the treprostinil or its derivative, prodrug, ester, or a pharmaceutically acceptable salt thereof, is in a form suitable for subcutaneous administration, continuous subcutaneous infusion, intravenously administration or inhalation. Subcutaneous formulations administered to the subject may include any of those described in U.S. Pat. No. 7,999,007 (including the commercial product Remodulin® (treprostinil) Injection), the entire disclosure of which is hereby incorporated by reference. In other kit embodiments, the treprostinil or its derivative, or a pharmaceutically acceptable salt thereof, is in an orally available form selected from the group consisting of tablets and capsules.

The effects of the method on pulmonary fibroses (PF) can be ascertained via an animal model of PF such as bleomycin and vanadium pentoxide (V205) models as described in Bonner J C, Rice A B, Ingram J L, Moomaw C R, Nyska A, Bradbury A, Sessoms A R, Chulada P C, Morgan D L, Zeldin D C, and Langenbach R. Susceptibility of cyclooxygenase-2-deficient mice to pulmonary fibrogenesis. *Am J Pathol* 161: 459-470, 2002; 23; and Keerthisingam C B, Jenkins R G, Harrison N K, Hernandez-Rodriguez N A, Booth H, Laurent G J, Hart S L, Foster M L, and McAnulty R J. Cyclooxygenase-2 deficiency results in a loss of the anti-proliferative response to transforming growth 31 factor-beta in human fibrotic lung fibroblasts and promotes bleomycin-induced pulmonary fibrosis in mice. *Am J Pathol* 158: 1411-1422, 2001, incorporated herein by reference in their entirety.

In preferred embodiments, treprostinil is administered via inhalation. Inhaled compositions comprising treprostinil may include sprays, aerosols, and dry powder compositions. Said compositions may include a variety of excipients. Inhalable compositions administered may include any of those described in U.S. Pat. No. 9,339,507 (including the commercial product Tyvaso® (treprostinil) Inhalation Solution), WO2017192993 and WO2014085813, the entire disclosures of which are hereby incorporated by reference.

The excipient or excipients of the pharmaceutical composition according to the invention may have water solubility greater than 5 g/l and often greater than 100 g/l and more. They are preferably chosen among sugars, salts or amino acids and have double function of minimizing the effect of the inhaled composition on the fluid's cellular outcome. Regarding the composition in its solid dry form, the excipient also forms the solid matrix in which the treprostinil, a prodrug, ester, salt, or derivative thereof is dispersed.

The composition may include excipients such as lactose, corn starch, or the like, glidants such as magnesium stearate, etc., emulsifying agents, suspending agents, stabilizers, and isotonic agents, etc. If desired, a sweetening agent and/or a flavoring agent may be added. Exemplary excipients include, without limitation, polyethylene glycol (PEG), hydrogenated castor oil (HCO), cremophors, carbohydrates, starches (e.g., corn starch), inorganic salts, antimicrobial agents, antioxidants, binders/fillers, surfactants, lubricants (e.g., calcium or magnesium stearate), glidants such as talc, disintegrants, diluents, buffers, acids, bases, film coats, combinations thereof, and the like. Other examples of soluble excipients that may be used in the composition according to the invention are alitame, acesulfame potassium, aspartame, saccharin, sodium saccharin, sodium cyclamate, sucralose, threalose, xylitol, citric acid, tartaric acid, cyclodextrins, dextrins, hydroxyethylcellulose, gelatine, malic acid, maltitol, maltodextrin, maltose, polydextrose, tartaric acid, sodium or potassium bicarbonate, sodium or potassium chloride, sodium or potassium citrate, phospholipids, lactose, sucrose, glucose, fructose, mannitol, sorbitol, natural aminoacids, alanine, glycine, serine, cysteine, phenylalanine, tyrosine, tryptophan, histidine, methionine, threonine, valine, isoleucine, leucine, arginine, lysine, aspartic acid, glutamic acid, asparagine, glutamine, proline, their salts, and their possible simple chemical modifications such as in N-acetylcysteine, and carbocysteine.

The preferred soluble excipients are alkaline metals salts such as sodium chloride or potassium chloride, and sugars, such as lactose. Specific carbohydrate excipients include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol, sorbitol (glucitol), pyranosyl sorbitol, myoinositol, and the like.

As far as the hollow morphology of the particles of the dry powder is concerned, the composition requires the presence of a soluble excipient, preferably a sugar like lactose, able to form in the beginning of the solvent evaporation phase during preparation of the composition, during spray-drying, the backbone of the particle, producing high porosity particles.

In some embodiments, the excipient comprises a surfactant. The surfactant of the composition can be chosen among different classes of surfactants of pharmaceutical use.

Surfactants suitable to be used in the present invention are all those substances characterized by medium or low molecular weight that contain a hydrophobic moiety, generally readily soluble in an organic solvent but weakly soluble or insoluble in water, and a hydrophilic (or polar) moiety, weakly soluble or insoluble in an organic solvent but readily soluble in water. Surfactants are classified according to their polar moiety. Therefore, surfactant with a negatively charged polar moiety are called anionic surfactants, while cationic surfactants have a positively charged polar moiety. Uncharged surfactant are generally called non-ionic, while surfactant charged both positively and negatively are called zwitterionic. Examples of anionic surfactants are salts of fatty acids (better known as soaps), sulfates, sulfate ethers and phosphate esters. Cationic surfactants are frequently based on polar groups containing amino groups. Most common non-ionic surfactants are based on polar groups containing oligo-(ethylene-oxide) groups. Zwitterionic surfactants are generally characterized by a polar group formed by a quaternary amine and a sulfuric or carboxylic group.

Specific examples of this application are the following surfactants: benzalkonium chloride, cetrimide, docusate sodium, glyceryl monolaurate, sorbitan esters, sodium lauryl sulfate, polysorbates, phospholipids, biliary salts.

Non-ionic surfactants, such as polysorbates and polyethylene and polyoxypropylene block copolymers, known as "Poloxamers," may be used. Polysorbates are described in the CTFA International Cosmetic Ingredient Dictionary as mixtures of sorbitol and sorbitol anhydride fatty acid esters condensed with ethylene oxide. Particularly preferred are non-ionic surfactants of the series known as "Tween," in particular the surfactant known as "Tween 80," a polyoxyethylensorbitan. Additional exemplary excipients include surfactants such as other polysorbates, e.g., "Tween 20" and pluronics such as F68 and F88 (both of which are available from BASF, Mount Olive, N.J.), sorbitan esters, lipids (e.g., phospholipids such as lecithin and other phosphatidylcholines, and phosphatidylethanolamines), fatty acids and fatty esters, steroids such as cholesterol, and chelating agents, such as EDTA, zinc and other such suitable cations.

The presence of a surfactant, and preferably of Tween 80, may be necessary to reduce electrostatic charges found in compositions without it, the flow of the powder and the maintenance of the solid state in a homogeneous way without initial crystallization. According to the present invention, phospholipids are included in the above-mentioned definition of surfactants or excipients.

The inhalatory formulation according administered can include a hydrophobic substance in order to reduce sensitivity to humidity. Such hydrophobic substance is preferably leucine, which makes the particle disaggregation easier.

In case of production of a solid product in powder form, this can occur using different techniques, well consolidated in the pharmaceutical industry. The preparation of fine particles through spray-drying represents a preferred method according to the invention. In case of industrial production, this technique is undoubtedly preferred to freeze-drying, which at the moment is the most expensive drying process, both for the apparatus used, and for the yield and production times.

The pharmaceutical composition according to the invention can include other components, such as pH buffers and preservatives. Buffers include, but are not limited to, citric acid, sodium chloride, potassium chloride, sodium sulfate, potassium nitrate, sodium phosphate monobasic, sodium phosphate dibasic, and combinations thereof.

Further, a composition administered may optionally include one or more acids or bases. Non-limiting examples of acids that can be used include those acids selected from

the group consisting of hydrochloric acid, acetic acid, phosphoric acid, citric acid, malic acid, lactic acid, formic acid, trichloroacetic acid, nitric acid, perchloric acid, phosphoric acid, sulfuric acid, fumaric acid, and combinations thereof. Non-limiting examples of suitable bases include bases selected from the group consisting of sodium hydroxide, sodium acetate, ammonium hydroxide, potassium hydroxide, ammonium acetate, potassium acetate, sodium phosphate, potassium phosphate, sodium citrate, sodium formate, sodium sulfate, potassium sulfate, potassium fumerate, and combinations thereof.

The excipients may include an antioxidant, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

The term “dry powder” in reference to the composition of the invention, refers to a powder, granulate, tablet form composition, or any other solid form with a humidity content that assures to the composition chemical stability in time. More precisely, the term “dry” refers to a solid composition with water content lower than 10% w/w, normally less than 5% and preferably less than 3%.

The amount of any excipient in the dry powder composition of the invention can change within a wide range. The amount of any individual excipient in the composition will vary depending on the role of the excipient, the dosage requirements of the active agent components, and particular needs of the composition. Generally, however, the excipient will be present in the composition in an amount of about 1% to about 99% by weight, preferably from about 5% to about 98% by weight, more preferably from about 15% to about 95% by weight of the excipient. In general, the amount of excipient present in a composition of the disclosure is selected from the following: at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or even 95% by weight.

The treprostinil composition administered may be provided as a kit that includes a metered dose inhaler containing a pharmaceutical composition comprising treprostinil or its derivative, ester, prodrug, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient’s breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with ILD that can be treated by treprostinil. In some cases, the kit is a kit for treating ILD, that includes (i) a metered dose inhaler containing a pharmaceutical composition comprising treprostinil or its derivative, ester, prodrug, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

The present disclosure also provides a method of treating a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia (low oxygen levels) by administering to a subject, such as a human being, with such the pulmonary hypertension an effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. Pulmonary hypertension due to a chronic lung disease and/or hypoxia belongs Group 3 pulmonary hypertension according to the World Health Organization (WHO) classification.

The chronic lung disease may include an obstructive lung disease in which the lung airways are narrow and make it difficult to exhale, such as chronic obstructive pulmonary disease (COPD) and emphysema; a restrictive lung disease in which the lungs have a difficult time expanding when one inhales, such as interstitial lung disease or pulmonary fibrosis; sleep apnea; living in an area of high altitude for a long period of time; and various combinations of the above conditions.

In some embodiments, the chronic lung disease may include idiopathic interstitial pneumonia, such as idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, respiratory bronchiolitis (e.g. respiratory bronchiolitis associated with interstitial lung disease), desquamative interstitial pneumonia, acute interstitial pneumonia; chronic hypersensitivity pneumonitis, occupational lung disease, pulmonary fibrosis, emphysema, connective tissue disease or any combination of the above conditions.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an increase, which may be statistically significant, in a six minute walk distance (6MWD) in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia compared to a baseline 6MWD value, i.e. a 6MWD value prior to the administering. For example, the 6MWD value may be statistically significantly increased after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide an increase of at least 5 m, at least 10 m or at least 15 m in the 6MWD compared to the baseline 6MWD value after at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide an increase of at least 5 m, at least 10 m, at least 15 m, at least 18 m or at least 20 m in the 6MWD compared to the baseline 6MWD value after at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an reduction, which may be statistically significant, in a plasma concentration of NT-proBNP in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia compared to a baseline NT-proBNP plasma concentration, i.e. a NT-proBNP plasma concentration value prior to the administering. For example, the NT-proBNP plasma concentration may be statistically significantly reduced after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks of the administering. In some embodiments, the administering may provide a reduction of at least 50 pg/ml, at least 100 pg/ml, at least 150 pg/ml, at least 200 pg/ml, at least 250 pg/ml, at least 300 pg/ml or at least 350 pg/ml in the NT-proBNP plasma concentration compared to

the baseline the NT-proBNP plasma concentration value after at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug to a subject with a pulmonary hypertension due to a chronic lung disease may provide a reduction, which may be statistically significant, of a number of exacerbation(s) of the chronic lung disease. For example, a number of exacerbation(s) of the chronic lung disease may be lower in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the number of exacerbation(s) may be lowered by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70% or at least 80%. The exacerbation(s) may include an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug to a subject with a pulmonary hypertension due to a chronic lung disease and/or hypoxia may provide a reduction, which may be statistically significant, of a number of clinical worsening event(s). For example, a number of clinical worsening event(s) may be lower in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the number of clinical worsening event(s) may be lowered by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70% or at least 80%. The clinical worsening event(s) may include one or more of hospitalization due to a cardiopulmonary indication, a decrease in a 6MWD by more than 15% from a baseline 6MWD value, death or a lung transplantation.

In some embodiments, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may provide an improvement, which may be statistically significant, in forced vital capacity (FVC) in a subject with a pulmonary hypertension due to a condition selected from a chronic lung disease and/or hypoxia. For example, the FVC may be higher in a patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug for at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks, or at least 20 weeks or at least 24 weeks or at least 28 weeks or at least 32 weeks or at least 36 weeks or at least 40 weeks or at least 44 weeks or at least 48 weeks or at least 52 weeks, compared to a patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. For example, the FVC value may be higher by at least 10 ml or at least 15 ml or at least 20 ml or at least 25 ml or at least 30 ml or at least 35 ml or at least 40 ml or at least 45 ml after at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks or at least 16 weeks of the administering in the patient subpopulation with the pulmonary hypertension due to the chronic lung disease and/or hypoxia, who was administered the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug compared to the patient subpopulation with the same condition, which was administered a placebo instead of treprostinil. In patients with a chronic lung disease, such as interstitial lung disease, and/or hypoxia, an FVC value usually decreases with time when untreated. Thus, administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt may increase an FVC value compared to an FVC value before the administering; maintain an FVC value within 5%, 10% or 20% within the FVC value prior to the administering; or reduce a decrease of an FVC value with time compared to a decrease in an FVC value with no administering the effective amount of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt, such a decrease in an FVC value when placebo is administered instead of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt.

In some embodiments, treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by inhalation, which may be, for example, an oral inhalation or a nasal inhalation. In some embodiments, treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by an inhalation device, which may be for example, a pulsed inhalation device, such as a metered dose inhaler and/or a pulsed nebulizer. Pulsed inhalation devices are disclosed, for example, in U.S. patent application publication No. 20080200449, U.S. Pat. Nos. 9,358,240; 9,339,507; 10,376,525; and 10,716,793, each of which is incorporated herein by reference in its entirety.

In some embodiments, the inhalation device, such as a pulsed inhalation device, may contain a solution or a suspension comprising treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. For example, such solution or suspension may be used for aerosolizing or a nebulizing by an inhalation device, such as a nebulizer and/or a metered dose inhaler. One example of a solution may be a commercial product Tyvaso®. A concentration of treprostinil in such solution may vary. In some embodiments, the treprostinil concentra-

tion may be from 200 μg/ml to 2000 μg/ml or from 300 μg/ml to 1500 μg/ml or from 400 μg/ml to 1200 μg/ml or any value or subrange within these ranges. For example, in a certain embodiment, the treprostinil concentration may be 600 μg/ml.

In some embodiments, the inhalation device, such as a pulsed inhalation device, may be a dry powder inhaler, which may contain a dry powder composition or formulation comprising treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug. For example, a dry powder inhaler and a dry powder composition or formulation comprising treprostinil are disclosed in WO2019/237028, which incorporated herein by reference in its entirety. In some embodiments, in addition to treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug, the dry powder composition may further a diketopiperazine, such as (E)-3,6-bis[4-(N-carbonyl-2-propenyl) amidobutyl]-2,5-diketopiperazine (FDKP).

Treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug may be administered by inhalation in a single administering event which may involve a limited number of breaths (or inhalations) by the subject. For example, in some embodiments, a number of breaths in the single administering event may not exceed 20 breaths (or inhalations) or 19 breaths (or inhalations) or 18 breaths (or inhalations) or 17 breaths (or inhalations) or 16 breaths (or inhalations) or 15 breaths (or inhalations) or 14 breaths (or inhalations) or 13 breaths (or inhalations) or 12 breaths (or inhalations) or 11 breaths (or inhalations) or 10 breaths (or inhalations) or 9 breaths (or breaths (or inhalations) inhalations) or 8 breaths (or inhalations) or 7 breaths (or inhalations) or 6 breaths (or inhalations) or 5 breaths (or inhalations) or 4 breaths (or inhalations) or 3 breaths (or inhalations) or 2 breaths (or inhalations) or 1 breath (or inhalation).

A dose of treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug administered by inhalation in a single administering event may vary. In some embodiments, the single administering event dose may be from 7.5 μg to 100 μg or 10 μg to 100 μg or 15 μg to 100 μg from 15 μg to 90 μg or from 15 μg to 75 μg or from 30 μg to 75 μg or any value or subrange within these ranges.

A number of single administering events per day for administering treprostinil, its prodrug, its pharmaceutically acceptable salt or a pharmaceutically acceptable salt of its prodrug administered by inhalation may vary. For example, the number of single administering events per day may be 1, 2, 3, 4, 5 or 6 per day.

The table below provides exemplary doses of treprostinil in a dry powder formulation, which may be used in a dry powder inhaler, and how they may compare with treprostinil doses in Tyvaso® inhalation solution.

DPI (treprostinil) Inhalation Powder Cartridge Strength (QID)	Tyvaso (treprostinil) Inhalation Solution Number of Breaths (QID)
16 mcg	2 to 4 (18 to 24 mcg)
32 mcg	5 to 7 (30 to 42 mcg)
48 mcg	8 to 10 (48 to 60 mcg)
64 mcg	11 to 13 (66 to 78 mcg)

The disclosure of all publications cited above are expressly incorporated herein by reference in their entireties to the same extent as if each were incorporated by reference individually.

The examples described herein are illustrative of the present invention and are not intended to be limitations thereon. Different embodiments of the present invention have been described according to the present invention. Many modifications and variations may be made to the techniques described and illustrated herein without departing from the spirit and scope of the invention. Accordingly, it should be understood that the examples are illustrative only and are not limiting upon the scope of the invention.

EXAMPLES

Example 1: Inhaled Treprostinil Results on Underlying Lung Disease

An exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (Collard et al., 2016). The present example shows that treatment with inhaled treprostinil resulted in significantly fewer exacerbations of underlying lung disease in patients.

Subjects having underlying lung disease were treated with inhaled treprostinil over 16 weeks. Subjects initiated inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Study drug doses were maximized throughout the study. Dose escalations (additional 1 breath 4 times daily) could occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated. Subjects were assessed during Screening and Baseline to determine eligibility for the study. Once eligible, 5 Treatment Phase visits to the clinic were required at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit). An Early Termination (ET) Visit was conducted for subjects who discontinued prior to Week 16; all assessments planned for the final Week 16 Visit were conducted during the ET Visit, if applicable. Subjects were contacted at least weekly by telephone or email to assess tolerance to study drug, adverse events (AEs), and changes to concomitant medications.

Efficacy assessments consisted of 6MWD, plasma NT-proBNP concentration, and time to clinical worsening. Exploratory endpoints included SGRQ, change in DSP, time to exacerbation of underlying disease, and pulmonary function tests. Safety assessments consisted of the development of AEs, vital signs, clinical laboratory parameters, ECG parameters, hospitalizations due to cardiopulmonary indications, exacerbations of underlying lung disease, and oxygenation.

Treatment resulted in significantly fewer exacerbations of underlying lung disease over the 16-week treatment period (26.4% in Inhaled Treprostinil group and 38.7% in placebo group; p=0.018) and decreased risk of an exacerbation of underlying lung disease (hazard ratio 0.66 or 34% reduction in risk) as shown in FIG. **1**.

In addition, the following FVC suggestive data was obtained from this study. Among patients treated with inhaled treprostinil, overall results from intent to treat group were:

Overall ITT
- 28.47 mL and 44.40 mL in FVC at Weeks 8 and 16
- Percent predicted FVC at Week 8 (1.79%; p=0.0139) and Week 16 (1.80%; p=0.0277).
- Subset IIP etiology:
  - 46.48 mL and 108.18 mL (p=0.0229) at Weeks 8 and 16
  - Percent predicted FVC at Week 8 (1.95%, p=0.0373) and Week 16 (2.88%; p=0.0096)
- Subset IPF etiology:
  - 84.52 mL and 168.52 mL (p=0.0108) at Weeks 8 and 16
  - Percent predicted FVC at Week 8 (2.54%; p=0.0380) and Week 16 (3.50%; p=0.0147)

Nintedanib: IPF~109 mL (3.2% predicted) at 52 weeks

Pirfenidone: IPF~153-193 mL at 52 weeks

Placebo corrected, rate of decline (not improvements)

In comparison to the known treatments for ILD (nintedanib and pirfenidone) shown above, inhaled treprostinil achieves comparable effects with shorter treatment duration.

Pulmonary function testing was initially conducted as a safety assessment (Safety Population) during the study. The results indicated that although most PFT parameters remained stable for subjects in the study, a notable improvement in FVC (% predicted) was observed at Week 16 in the inhaled treprostinil group (median improvement of 1.0% compared to a 1.0% reduction in the placebo group). As a result, post hoc MMRM analyses of FVC data were performed for the ITT Population and are presented in Table 1 (ITT Population), Table 2 (by PH ILD Etiology of IIP) and Table 3 (for subjects with IPF), shown below.

TABLE 1

Analysis of FVC Data Using Mixed Model Repeated Measurement - ITT Population

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
				FVC (mL)			
Week 8	Inhaled treprostinil	142	5.49	Inhaled treprostinil − Placebo	28.47	−30.81, 87.74	0.3453
	Placebo	141	−22.98				
Week 16	Inhaled treprostinil	130	9.77	Inhaled treprostinil − Placebo	44.40	−25.25, 114.05	0.2106
	Placebo	126	−34.63				
				FVC (% predicted)			
Week 8	Inhaled treprostinil	142	0.77	Inhaled treprostinil − Placebo	1.79	0.37, 3.21	0.0139
	Placebo	141	−1.02				
Week 16	Inhaled treprostinil	130	1.07	Inhaled treprostinil − Placebo	1.80	0.20, 3.39	0.0277
	Placebo	126	−0.72				

Abbreviations:
CI, confidence interval;
FVC, forced vital capacity;
ITT, Intent-to-Treat;
LS, least square;
MMRM, mixed model repeated measurement
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

TABLE 2

Analysis of FVC Data Using Mixed Model Repeated Measurement for PH-ILD Etiology of IIP - ITT Population

Visit	Treatment	N	LS Mean	Contrast	Estimated Difference	95% CI	p-value
				PH-ILD Etiology: IIP FVC (mL)			
Week 8	Inhaled treprostinil	58	9.27	Inhaled treprostinil − Placebo	46.48	−32.55, 125.51	0.2467
	Placebo	71	−37.21				
Week 16	Inhaled treprostinil	52	22.16	Inhaled treprostinil − Placebo	108.18	15.25, 201.10	0.0229
	Placebo	63	−86.02				
				FVC (% predicted)			
Week 8	Inhaled treprostinil	58	0.92	Inhaled treprostinil − Placebo	1.95	0.12, 3.79	0.0373
	Placebo	71	−1.03				
Week 16	Inhaled treprostinil	52	1.66	Inhaled treprostinil − Placebo	2.88	0.72, 5.05	0.0096
	Placebo	63	−1.23				

Abbreviations:
CI, confidence interval;
CPFE, combined pulmonary fibrosis and emphysema;
CTD, connective tissue disease;
FVC, forced vital capacity;
ILD, interstitial lung disease;
IIP, idiopathic interstitial pneumonia;
ITT, Intent-to-Treat;
LS, least square;
MMRM, mixed model repeated measurement
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Table 3: Analysis of FVC Data Using Mixed Model Repeated Measurement for Subjects with IPF - ITT for IIP Subjects

IPF FVC (mL)							
Week 8	Inhaled treprostinil	31	41.69	Inhaled treprostinil - Placebo	84.522	−20.409, 189.454	0.1128
	Placebo	47	−42.83				
Week 16	Inhaled treprostinil	28	38.24	Inhaled treprostinil - Placebo	168.524	40.078, 296.970	0.0108
	Placebo	42	−130.3				
FVC (% predicted)							
Week 8	Inhaled treprostinil	31	1.60	Inhaled treprostinil - Placebo	2.543	0.145, 4.941	0.0380
	Placebo	47	−0.94				
Week 16	Inhaled treprostinil	28	1.62	Inhaled treprostinil - Placebo	3.504	0.712, 6.295	0.0147
	Placebo	42	−1.88				

Abbreviations:
CI, confidence interval;
FVC, forced vital capacity;
IPF, idiopathic pulmonary fibrosis;
ITT, Intent-to-Treat;
LS, least square; MMRM, mixed model repeated measurement
LSMean, p-values, estimated difference, and associated 95% CI were from the MMRM with the change from baseline in FVC/% predicted FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; baseline FVC/% predicted FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Treatment with inhaled treprostinil resulted in improvements of 28.47 mL and 44.40 mL in FVC at Weeks 8 and 16, respectively; significant when presented as % predicted FVC at Week 8 (1.79%; p=0.0139) and Week 16 (1.80%; p=0.0277).

When FVC was analyzed by PH-ILD etiology of IIP, treatment with inhaled treprostinil resulted in improvements of 46.48 mL and 108.18 mL (p=0.0229) when compared to placebo at Weeks 8 and 16, respectively. The between group differences for % predicted FVC were statistically significant at Week 8 (1.95%, p=0.0373) and Week 16 (2.88%; p=0.0096).

Further analysis of FVC for subjects with an IPF etiology (using only the IIP subjects in the ITT Population), showed that treatment with inhaled treprostinil resulted in improvements of 84.52 mL and 168.52 mL (p=0.0108) compared to placebo at Weeks 8 and 16, respectively. The between group differences for % predicted FVC were statistically significant at Week 8 (2.54%; p=0.0380) and Week 16 (3.50%; p=0.0147).

Example 2

The following prophetic example will assess efficacy of treprostinil as indicated for the treatment of chronic fibrosing interstitial lung diseases (CF-ILDs) including Idiopathic Interstitial Pneumonias (IIPs) including IPF, chronic hypersensitivity pneumonitis (CHP), and environmental/occupational fibrosing lung disease.

Patients may be treated with inhaled treprostinil up to 15 breaths QID based upon tolerability. Change from baseline to Week 24 of treatment in FVC (absolute or percent predicted) as primary efficacy endpoint will be assessed. Parameters that may be assessed include time to exacerbation of underlying lung disease, 6 meter walk distance test (6MWD), all-cause mortality/survival, time to death, additional analyses of FVC (e.g. absolute and relative change), changes from baseline in SpO_2, diffusing capacity of the lungs for carbon monoxide (DLCO), NT-proBNP, and King's Brief Interstitial Lung Disease Questionnaire.

REFERENCES

1. Collard et al., *American Journal of Respiratory and Critical Care Medicine*, Volume 194 Number 3, pg. 265.

2. Meyer et al., (Apr. 3, 2017). *Therapeutics and Clinical Risk Management.* 13: 427-437.

Example 3: Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

Methods

We enrolled patients with interstitial lung disease and pulmonary hypertension (documented by right heart catheterization) in a multicenter, randomized, double-blind, placebo-controlled, 16-week trial. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total, 72 μg) four times daily, or placebo. The primary efficacy end point was the difference between the two treatment groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary end points included the change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

Results

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61;

95% CI, 0.40 to 0.92; P=0.04 by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

Conclusions

In patients with pulmonary hypertension due to interstitial lung disease, inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with placebo.

Precapillary pulmonary hypertension is defined as an elevation in mean pulmonary arterial pressure and pulmonary vascular resistance.[1] In the World Health Organization (WHO) classification of pulmonary hypertension, precapillary pulmonary hypertension due to lung disease is classified as group 3. The most common lung diseases associated with group 3 pulmonary hypertension are chronic obstructive pulmonary disease and interstitial lung disease.

Pulmonary hypertension has been reported in up to 86% of patients with interstitial lung disease and is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death.[2-4] Despite the global prevalence and poor clinical course of pulmonary hypertension due to interstitial lung disease, there are currently no approved therapies for these patients. Although data are limited, therapies approved for group 1 pulmonary hyper-tension (pulmonary arterial hypertension) have been used to treat group 3 pulmonary hypertension.[5] Previous studies of vasodilator therapies have shown conflicting results. The largest trial to date evaluated the soluble guanylate cyclase stimulator riociguat in a patient population with group 3 pulmonary hypertension and was stopped early owing to serious harm.[6] Treprostinil is a stable analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.[7] An inhaled formulation of treprostinil was previously shown to improve exercise capacity after 12 weeks of therapy in patients with group 1 pulmonary hypertension.[8] Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension.[9-12] Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.

Trial Design and Oversight

INCREASE was a multicenter, randomized, double-blind, placebo-controlled trial. The trial was monitored by an independent data and safety monitoring committee and was conducted in accordance with Good Clinical Practice guidelines.

Trial Population

The trial population consisted of patients 18 years of age or older in whom interstitial lung disease was diagnosed on the basis of evidence of diffuse parenchymal lung disease on computed tomography of the chest (not centrally adjudicated) performed within 6 months before randomization. Confirmation of group 3 pulmonary hypertension by right heart catheterization within 1 year before randomization was required. Group 3 pulmonary hypertension was defined by pulmonary vascular resistance of more than 3 Wood units, pulmonary capillary wedge pressure of 15 mm Hg or lower, and mean pulmonary arterial pressure of 25 mm Hg or higher. Patients with group 3 pulmonary hypertension due to connective tissue disease were also required to have a baseline forced vital capacity of less than 70%. Eligible patients also had to walk at least 100 m during a 6-minute walk test. Patients receiving drug treatment (i.e., pirfenidone or nintedanib) for their underlying lung disease were required to have been receiving a stable dose for at least 30 days before undergoing randomization. Patients receiving approved therapy for pulmonary arterial hypertension within 60 days before randomization were not eligible for enrollment. Written informed consent was obtained from all the patients.

TABLE 4

Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Female sex - no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) - yr	65.6 (26-90)	67.4 (36-85)	66.5 (26-90)
Age distribution - no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group - no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.03)
Hispanic or Latino ethnic group - no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis - yr	0.54 ± 1.16	0.54 ± 1.31	0.54 ± 1.23

TABLE 4-continued

Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Cause of lung disease - no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory - no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen - no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy - no (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

*Plus-minus values are means ± SD. Additional patient characteristics at baseline are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
†Race and ethnic group were reported by the patient.

Trial Procedures

Within 30 days after screening, eligible patients were randomly assigned in a 1:1 ratio to receive inhaled treprostinil (Tyvaso, United Therapeutics) or placebo in a double-blind manner. Randomization, based on permuted blocks, was stratified by baseline 6-minute walk distance (≤350 m vs. >350 m) and was implemented through an interactive Web-response system.

Inhaled treprostinil (0.6 mg per milliliter) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 µg per breath. Placebo was administered similarly as a visually identical solution. The first dose of trial drug (3 breaths) was administered in the clinic, followed by at least a 1-hour observation period. The dose of treprostinil or placebo was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maxi-mum dose of 12 breaths four times daily. Investigators adjusted the dose on an individual patient basis to achieve the maximum tolerated dose leading to functional improvement.

Trial Assessments

The 6-minute walk test was performed and laboratory data were obtained at baseline and at weeks 4, 8, 12, and 16, or at the time of early discontinuation of treprostinil or placebo. Each 6-minute walk test was performed 10 to 60 minutes after the most recent dose of active drug or placebo, which is the time of peak plasma treprostinil exposure. A trough test was performed at week 15 at least 4 hours after the participant received a dose of treprostinil or placebo and at least 24 hours before the week 16 test. Pulse oximetry was performed immediately before, during, and after each 6-minute walk test. Measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and pulmonary function tests were performed at baseline and at weeks 8 and 16 (or at early discontinuation) after the patients recovered from the 6-minute walk test. The St. George's Respiratory Questionnaire (SGRQ), a quality-of-life measure, was completed at baseline and week 16 or at the time of early discontinuation.

Outcome Measures

The primary end point of the trial was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary efficacy end points were analyzed in the following hierarchical testing order: the change in NT-proBNP level from baseline to week 16, the time to clinical worsening, the change in 6-minute walk distance at peak plasma treprostinil level at week 12, and the change in 6-minute walk distance at trough treprostinil level at week 15. The time to clinical worsening was evaluated from the time of randomization until the patient's withdrawal from the trial and was defined as the time until the occurrence of any one of the following events: hospitalization for a cardiopulmonary indication, a decrease in 6-minute walk distance greater than 15% from baseline that was directly related to the disease under study at two consecutive visits and at least 24 hours apart, death from any cause, or lung transplantation.

Exploratory end points were the changes in peak 6-minute walk distance at weeks 4 and 8, quality of life as measured with the use of the SGRQ at week 16, and the distance-saturation product (calculated by multiplying the total distance walked by the lowest oxygen saturation measurement during the 6-minute walk) at week 16. Safety end points included adverse events, abnormal laboratory results, oxy-

genation as measured by pulse oximetry (Spo2) and supplemental oxygen requirement, changes in pulmonary function test results, hospitalization for a cardiopulmonary indication, and investigator-reported exacerbations of underlying lung disease, defined as acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

Statistical Analysis

Original estimates suggested that with 266 patients randomly assigned in a 1:1 ratio to receive inhaled treprostinil or placebo, the trial would have at least 90% power at a significance level of 0.05 (two-sided) to detect a between-group difference of 30 m in the change in peak 6-minute walk distance from baseline at week 16, assuming a standard deviation of 75 m. To account for approximately 15% of participants discontinuing the trial, 314 patients would need to be enrolled.

For the primary efficacy analysis, the change in 6-minute walk distance was analyzed by mixed-model repeated-measures methods, under the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed by means of a multiple imputation approach with a multivariate normal imputation model according to the Markov chain Monte Carlo method. The imputation model included treatment group, all scheduled visits, the patient's sex, and the patient's age at randomization. If the result for the primary efficacy end point was significant, secondary efficacy end points were to be evaluated according to a hierarchical testing procedure. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects for secondary efficacy end points.

Results

Patients

Of 462 patients screened for eligibility, 326 were enrolled at 93 centers and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients) (FIG. **2**). Baseline characteristics were similar in the two groups (Table 4). The mean age of the patients was 66.5 years, 46.9% were female, and the most common diagnosis was idiopathic interstitial pneumonia (in 44.8%). At baseline, the mean 6-minute walk distance was 259.6 m, the mean pulmonary vascular resistance was 6.2 Wood units, and the mean NT-proBNP level was 1832.9 pg per milliliter.

Exposure and Follow-up

Patients in the treprostinil group took a median of 11 breaths from the inhaler (66 μg) at each of four daily sessions at week 12 and 12 breaths (72 μg) per session at week 16. The percentage of patients in this group who took 10 to 12 breaths (60 to 72 μg) per session was 57.0% at week 12 and 57.8% at week 16. Patients in the placebo group took a median of 12 breaths from the inhaler per session at weeks 12 and 16.

Forty patients assigned to receive inhaled treprostinil (24.5%) and 38 assigned to placebo (23.3%) discontinued the assigned regimen pre-maturely. These patients were encouraged to remain in the trial and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued participation in the trial. The reasons for discontinuation are shown in FIG. **2**.

Primary End Point

Mean within-group changes in the 6-minute walk distance are shown in FIG. **2**. Mixed-model repeated-measures analysis showed that the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001) (Table 5 and FIG. **4**). Similar effects were observed across subgroups, including subgroups defined by disease cause and severity (as measured by baseline 6-minute walk distance), baseline hemodynamics, and dose group (FIG. **5**). In addition, the between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41; P<0.001) (FIG. **6**).

TABLE 5

Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 - m†	21.08 ± 5.12	−10.04 ± 5.12	31.12 ± 7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change - pg/ml	−396.35 ± 1904.90	1453.95 ± 7296.20		
Median - pg/ml	−22.65	20.65		
Range - pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85 ± 0.06	1.46 ± 0.11	±0.58 ± 0.06 (0.47 to 0.72)‖	<0.001

TABLE 5-continued

Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	Treatment Effect (95% CI)	P Value
Occurrence of clinical worsening - no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6 minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6- minute walk distance from baseline to wk 12 - m†	18.77 ± 4.99	−12.52 ± 5.01	31.29 ± 7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6- minute walk distance from baseline to wk 15 - m	9.3 ± 5.5	−12.7 ± 5.5	21.99 ± 7.7± (6.85 to 37.14)†	0.005††

*Plus-minus values are means ± SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide.

†The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.

‡This is a least-squares mean difference between the groups.

§The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.

¶The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.

||This is the treatment ratio, which is the ratio of ratios between two treatment groups.

**This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

††The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

Secondary and Exploratory End Points

Patients assigned to inhaled treprostinil, as compared with those assigned to placebo, showed significant improvements in each of the secondary end points (Table 5). The NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001) (FIG. **7**). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test) (FIG. **1**). The least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group (P<0.001), and the change from baseline to week 15 in trough 6-minute walk distance was 21.99 m greater in the treprostinil group (P=0.004). There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance-saturation product at week 16.

Safety End Points

TABLE 6

Summary of Adverse Events

Variable	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event - no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event - no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events - no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99

TABLE 6-continued

Summary of Adverse Events			
Variable	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	P Value*
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

*P values were calculated with the use of Fisher's exact test.

‡Shown are the most frequently occurring adverse events occurring in more than 10% of patients in either group in the safety population, which comprised all patients who underwent randomization and received at least one dose of treprostinil or placebo.

The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea (Table 6). Most of these events were of mild-to-moderate intensity.

Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo. No serious adverse events were reported significantly more frequently in the treprostinil group than in the placebo group.

Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P=0.02 by Fisher's exact test). Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%]; P=0.41). Inhaled treprostinil had no deleterious effect on any pulmonary function test variable during the trial. There were no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the trial period.

Discussion

Pulmonary hypertension frequently complicates the treatment of patients with interstitial lung disease and is associated with worse functional status, greater need for supplemental oxygen, and worse outcomes.[3, 13] In the INCREASE trial, patients treated with inhaled treprostinil had significant improvements in exercise capacity, as evidenced by changes in the 6-minute walk distance. Treatment with inhaled treprostinil was also associated with a lower risk of clinical worsening than that in patients who received placebo, as well as reductions in NT-proBNP levels and fewer exacerbations of underlying lung disease, over the 16-week treatment period. The safety profile of inhaled treprostinil observed in this vulnerable patient population was similar to that reported in previous studies. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. The use of inhaled treprostinil was not associated with any decrement in lung function.

Patients with group 3 pulmonary hypertension are often treated with systemic pulmonary vasodilators, which are currently approved only for treatment of group 1 pulmonary hypertension. However, there is concern that such agents could worsen ventilation-perfusion matching in patients with group 3 pulmonary hypertension. Inhaled agents have the advantage of preferentially redirecting blood flow to the best-ventilated lung units, thus reducing the risk of ventilation-perfusion mismatching.[9, 14] Indeed, a retrospective study of inhaled treprostinil in patients with group 3 pulmonary hypertension showed that such patients had improvements in functional class and 6-minute walk distance without any adverse effect on peripheral oxygen saturation, rein-forcing the concept of unchanged or even improved ventilation-perfusion matching with inhaled treprostinil.[10] Similarly, in the current trial, we found no evidence of worsened oxygenation, which further allays concerns about ventilation-perfusion mismatching.

The INCREASE trial was not without its limitations. The trial was of short duration, and 21% of the patients discontinued the trial prematurely (before week 16). In addition, events of clinical worsening and exacerbation of underlying lung disease were investigator-reported and not adjudicated by an independent review committee. Finally, the size of the favorable treatment effect on the 6-minute walk distance with inhaled treprostinil is similar to estimates of the minimum clinically important difference for this test in patients with pulmonary disease (21.7 to 37 m in a study by Nathan et al., and 24 to 45 m in a study by du Bois et al.).[15, 16]

This study showed that among patients with pulmonary hypertension due to interstitial lung disease, treatment with inhaled treprostinil improved exercise capacity as shown by improvement in the 6-minute walk distance through the end of the 16-week treatment period. In addition, treatment with inhaled treprostinil was associated with a lower risk of clinical worsening than that with placebo, a reduction in NT-proBNP levels, and fewer exacerbations of underlying lung disease.

Supplemental Information

TABLE 7

Additional Baseline Patient Characteristics.			
	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
6-minute walk distance, meters;	254.1 (100-538)	265.1 (30-505)	259.6 (30-538)
mean (range) Median	256.0	260.0	259.0
Pulmonary vascular resistance,	6.369 (3.11-8.05)	6.013 (3.06-17.62)	6.191 (3.06-18.05)
Woods units; mean (range) Median	5.570	5.060	5.275
NT-proBNP, pg/mL; mean (range)	1857.53 (10.2-21942.0)	1808.86 (23.0-16297.0)	1832.88 (10.2-21942.0)

TABLE 7-continued

Additional Baseline Patient Characteristics.

	Inhaled Treprostinil (N = 163)	Placebo (N = 163)	All Patients (N = 326)
Median*	550.50	420.80	503.85
Pulmonary arterial pressure, mmHg; mean (range	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
Pulmonary capillary wedge pressure, mmHg; mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV1% Predicted; mean (range)	63.9 (23, 120)	65.0 (22, 145)	
Median	63.0	63.0	
FVC % Predicted; mean (range)	62.5 (24, 130)	63.8 (20, 134)	
Median	60.0	61.0	
TLC % Predicted; mean (range)	62.9 (25, 126)	64.2 (30, 109)	
Median	62.0	62.5	
DLCO % Predicted; mean (range)	30.0 (5, 86)	28.1 (1, 86)	
Median	29.0	26.0	

DLCO, lung diffusion capacity;
FEV1, forced expiratory volume in 1 second;
FVC, forced vital capacity;
NT-proBNP, N-terminal pro-brain natriuretic peptide;
TLC, total lung capacity
*N = 156 inhaled treprostinil; N = 160 placebo

TABLE 8

St. George's Respiratory Questionnaire Results.

	Inhaled Treprostinil N = 163		Placebo N = 163	
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline
Baseline				
n	143		134	
Mean (SD)	57.17 (15.77)		57.67 (15.78)	
Median	59.80		56.30	
Interquartile	45.60, 67.90		46.50 70.70	
Min, Max	14.7, 94.9		18.4 88.6	
Week 16				
n	143	143	134	134
Mean (SD)	55.91 (17.07)	−1.25 (10.99)	57.49 (15.33)	−0.18 (10.72)
Median	56.30	−0.70	55.50	0.10
Interquartile	40.50, 67.00	−7.10, 5.20	46.80 69.70	−6.50, 6.10
Min, Max	3.5, 92.0	−40.4, 29.0	16.9 96.5	−31.9, 33.3
LS Mean (SE)		−1.30 (0.87)		−0.13 (0.90)
LS Mean Difference (SE) and (95% CI)		−1.18, (1.25) (−3.63, 1.28)		

ANCOVA, analysis of covariance;
CI, confidence interval;
LS Mean, least squares mean;
SD, standard deviation;
SE, standard error

The St. George's Respiratory Questionnaire has a range of results from 0 to 100, with higher scores indicating greater impairment and with a minimum clinically important difference of 4 points.

The changes from baseline in Total Score and each of the 3 domain scores were analyzed by parametric ANCOVA with no imputation for missing data.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE S4

Distance Saturation Product Results by Study Visit (m %).

Visit/Variable Statistic	Inhaled Treprostinil N = 163	Placebo N = 163
Baseline		
n	118	109
Mean (SD)	208.140 (81.130)	218.247 (77.405)
Median	201.320	215.760
Interquartile	150.060, 256.750	170.800, 268.800
Min, Max	77.04, 421.07	63.00, 417.35
Week 16 Change from Baseline		
n	118	109
Mean (SD)	7.607 (45.680)	−4.803 (53.026)
Median	8.385	−1.950
Interquartile	−12.960, 34.890	−38.180, 32.000
Min, Max	−217.26, 117.42	−184.85, 129.28
LS Mean (SE)	7.2 (4.5)	−4.3 (4.7)
LS Mean Difference (SE) and 95% CI	11.51 (6.5), 95% CI (−1.33, 24.35)	

ANCOVA, analysis of covariance;
CI, confidence interval;
LS Mean, least squares mean;
SD, standard deviation;
SE, standard error;
SpO_2, saturation of peripheral capillary oxygenation

Change in distance saturation product is the product of distance walked and lowest SpO_2 recorded during the 6-minute walk test.[7] Change from baseline to Week 16 in distance saturation product was analyzed by parametric ANCOVA with no imputation for missing distance saturation product values.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE 9

Serious Adverse Events by Preferred Term

Serious Adverse Events	Inhaled treprostinil N = 163 n	Placebo N = 163 n
Any Serious Event	53 events in 38 patients (23.3%)	89 events in 42 patients (25.8%)
Acute respiratory failure	4	5
Death with unknown cause	3	1
Dyspnoea	3	7
Interstitial lung disease	3	2
Bronchitis	2	1
Chronic obstructive pulmonary disease	2	2
Chronic respiratory failure	2	0
Respiratory failure	2	5
Upper respiratory tract infection	2	1
Acute myocardial infarction	1	2
Acute right ventricular failure	1	0
Arrhythmia	1	0
B-cell lymphoma	1	0
Bronchopulmonary aspergillosis	1	0
Cardiac arrest	1	2
Cardiac failure congestive	1	2
Cardiopulmonary failure	1	0
Cellulitis	1	0
Cerebral haemorrhage	1	0
Chest pain	1	1
Combined pulmonary fibrosis and emphysema	1	0
Cor pulmonale	1	0
Haemoptysis	1	0
Hyperglycaemia	1	0
Hypervolaemia	1	0
Hypoxia	1	0
Idiopathic pulmonary fibrosis	1	4
Influenza	1	1
Left ventricular failure	1	0
Pain in extremity	1	0
Pneumonia	1	9
Pneumothorax	1	1
Pulmonary hypertension	1	1
Pulmonary oedema	1	0
Rhinovirus infection	1	0
Right ventricular failure	1	2
Syncope	1	1
Tachycardia	1	0
Abdominal pain	0	2
Acute kidney injury	0	1
Aspiration	0	1
Atrial fibrillation	0	1
Bradycardia	0	1
Cardiac failure	0	2
Cardiac failure acute	0	1
Cardiogenic shock	0	1
Chronic right ventricular failure	0	1
Coagulopathy	0	1
Cor pulmonale acute	0	1
Coronary artery disease	0	1
Disease progression	0	2
Epistaxis	0	1
Fluid overload	0	4
Haematochezia	0	1
Hypertension	0	1
Lumbar vertebral fracture	0	1
Metabolic encephalopathy	0	1
Pain	0	1
Pneumonia influenzal	0	1
Post procedural infection	0	1
Presyncope	0	2
Pulmonary congestion	0	1
Respiratory distress	0	1
Scleroderma	0	1
Sepsis	0	2
Transplant dysfunction	0	1
Urosepsis	0	1

TABLE 10

Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.

Variable Visit Treatment	N	LS Mean	Contrast: Inhaled treprostinil − Placebo Estimated Difference (95% CI)	P-value
FVC (mL)				
Week 8				
Inhaled treprostinil	142	5.49	28.47	0.35
Placebo	141	−22.98	(−30.81, 87.74)	
Week 16				
Inhaled treprostinil	130	9.77	44.40	0.21
Placebo	126	−34.63	(−25.25, 114.05)	
FVC (% predicted)				
Week 8				
Inhaled treprostinil	142	0.77	1.79	
Placebo	141	−1.02	(0.37, 3.21)	0.01
Week 16				
Inhaled treprostinil	130	1.07	1.80	0.03
Placebo	126	−0.72	(0.20, 3.39)	
FEV1 (mL)				
Week 8				
Inhaled treprostinil	142	−21.34	−8.95	0.72
Placebo	141	−12.39	(−57.16, 39.26)	
Week 16				
Inhaled treprostinil	130	−32.18	−2.56	0.93
Placebo	126	−29.62	(−57.67, 52.55)	
FEV1 (% predicted)				
Week 8				
Inhaled treprostinil	142	−0.18	0.57	0.43
Placebo	141	−0.75	(−0.83, 1.96)	
Week 16				
Inhaled treprostinil	130	−0.24	0.38	0.65
Placebo	126	−0.62	(−1.25, 2.01)	
TLC (mL)				
Week 8				
Inhaled treprostinil	135	−38.75	−16.23	0.80
Placebo	136	−22.51	(−141.9, 109.41)	
Week 16				
Inhaled treprostinil	127	45.43	17.37	0.85
Placebo	116	28.06	(−158.9, 193.61)	
TLC (% predicted)				
Week 8				
Inhaled treprostinil	135	−0.05	0.28	0.76
Placebo	136	−0.32	(−1.49, 2.05)	
Week 16				
Inhaled treprostinil	127	2.52	1.49	0.34
Placebo	116	1.03	(−1.57, 4.54)	
DLCO (mL/min/mmHg)				
Week 8				
Inhaled treprostini	136	−0.27	0.19	0.56
Placebo	136	−0.47	(−0.45, 0.84)	
Week 16				
Inhaled treprostinil	128	−0.61	0.02	0.96
Placebo	112	−0.63	(−0.73, 0.76)	
DLCO (% predicted)				
Week 8				
Inhaled treprostinil	136	−0.13	1.07	0.13
Placebo	136	−1.20	(−0.32, 2.47)	
Week 16				
Inhaled treprostinil	128	−1.14	0.60	0.44
Placebo	112	−1.74	(−0.93, 2.14)	

CI, confidence interval;
DLCO, diffusing capacity of the lungs for carbon monoxide;
FEV1, forced expiratory volume in 1 second;
FVC, forced vital capacity;
TLC, total lung capacity;;
LS Mean, least squares mean;
SE, standard error;
TLC, total lung capacity

LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in pulmonary function test parameter as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline measurement as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

The confidence intervals and p-values have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

TABLE 11

SpO_2 (%) Measured by Pulse Oximetry Results at Baseline and Week 16.

	Inhaled Treprostinil N = 163		Placebo N = 163		
Visit Statistic	Value	Change from Pre- walk	Value	Change from Pre- Walk	P-value*
Baseline Pre-walk SpO_2 (%)					
n	163		162		
Mean (SD)	95.3 (3.95)		94.5 (4.81)		
Median	96.0		96.0		
Min, Max	72, 100		68, 100		

TABLE 11-continued

SpO$_2$ (%) Measured by Pulse Oximetry Results at Baseline and Week 16.

	Inhaled Treprostinil N = 163		Placebo N = 163		
Visit Statistic	Value	Change from Pre- walk	Value	Change from Pre- Walk	P-value*
Baseline During Walk SpO$_2$ (%)					
n	154	154	153	153	0.13
Mean (SD)	80.3 (8.22)	−15.0 (7.87)	78.5 (8.20)	−16.1 (7.76)	
Median	81.0	−14.0	78.0	−15.0	
Min, Max	53, 99	−41, 2	53, 98	−39, 4	
Baseline Post-walk SpO$_2$ (%)					
n	163	163	162	162	0.17
Mean (SD)	85.3 (7.31)	−9.9 (6.50)	83.7 (8.74)	−10.9 (8.06)	
Median	86.0	−10.0	83.5	−11.0	
Min, Max	59, 100	−26, 5	57, 99	−39, 7	
Week 16 Pre-walk SpO$_2$ (%)					
n	130		122		
Mean (SD)	94.5 (4.35)		94.5 (4.22)		
Median	95.0		95.0		
Min, Max	74, 100		78, 100		
Week 16 During Walk SpO$_2$ (%)					
n	123	123	114	114	0.27
Mean (SD)	76.8 (7.70)	−17.6 (7.01)	78.2 (9.28)	−16.6 (9.04)	
Median	77.0	−17.0	79.0	−16.0	
Min, Max	46, 99	−38, −1	28, 98	−61, −1	
Week 16 Post-walk SpO$_2$ (%)					
n	128	128	122	122	0.07
Mean (SD)	82.1 (9.24)	−12.4 (8.05)	83.7 (7.75)	−10.8 (7.09)	
Median	83.0	−13.0	84.0	−11.5	
Min, Max	51, 100	−29, 3	65, 100	−31, 6	

SD, standard deviation;

SpO$_2$, saturation of peripheral capillary oxygenation

*P-values are calculated from analysis of covariance with change from pre-walk as dependent variable, treatment as fixed effect, and baseline SpO$_2$ as covariate.

TABLE 12

Supplemental Oxygen Use (L/min) at Baseline and Week 16.

	Inhaled Treprostinil N = 163		Placebo N = 163		
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline	P-value*
Baseline Pre-walk (L/min)					
n	163		163		
Mean (SD)	2.7 (2.2)		2.4 (2.0)		
Median	3.0		2.0		
Min, Max	0, 10		0, 8		
Baseline During Walk (L/min)					
n	163		163		
Mean (SD)	4.9 (4.0)		4.5 (3.8)		
Median	4.0		4.0		
Min, Max	0, 25		0, 15		
Week 16 Pre-walk (L/min)					
n	131	131	129	129	0.18
Mean (SD)	3.0 (2.5)	0.4 (1.4)	2.9 (2.4)	0.6 (1.3)	
Median	3.0	0.0	3.0	0.0	
Min, Max	0, 10	−3, 6	0, 10	−3, 5	

TABLE 12-continued

Supplemental Oxygen Use (L/min) at Baseline and Week 16.

	Inhaled Treprostinil N = 163		Placebo N = 163		
Visit Statistic	Value	Change from Baseline	Value	Change from Baseline	P-value*
Baseline During Walk (L/min)					
n	129	129	123	123	0.39
Mean (SD)	4.9 (4.0)	0.1 (0.8)	4.6 (3.7)	0.1 (0.3)	
Median	4.0	0.0	4.0	0.0	
Min, Max	0, 25	−2, 8	0, 15	0, 3	

SD, standard deviation

Subjects who did not use supplemental oxygen were coded as 0 in the summaries.

Subjects who received supplemental oxygen during the Baseline 6-minute walk test continued to receive the same flow rate at all subsequent 6-minute walk test assessments.

*P-values are calculated from analysis of covariance with change from baseline as dependent variable, treatment as fixed effect, and baseline oxygen use as covariate.

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Example 4. Aerosolized and Powder Inhaled Treprostinil

Randomized, 6-treatment, 6-period, 6-sequence, cross-over study (6×6 Williams design) in 36 healthy volunteers was performed to compare nebulized inhaled treprostinil administered by Tyvaso® nebulizer and Treprostinil inhalation powder (TreT) administered via a dry powder inhaler (published US Patent Application 20190321290). 4 subjects discontinued the study early (COVID-19, n=2; withdrawal by subject, n=1; non-compliance with study requirements, n=1).

Tyvaso Dose	TreT Dose
18 μg (3 nebulizer breaths)	16 μg cartridge
54 μg (9 nebulizer breaths)	48 μg cartridge
72 μg (12 nebulizer breaths)	64 μg cartridge

TABLE 14

Pharmacokinetic results for various doses for Tyvaso and TreT administered treprostinil. See also FIG. 9 and 10.

Comparison	Parameter	Geometric LSM (TreT) [CV %]	Geometric LSM (Tyvaso) [CV %]	Geometric LSM Ratio (%) [TreT/Tyvaso]	90% Confidence Interval
TreT 16 μg vs. Tyvaso 18 μg	AUC0-5	0.268 [24.1%]	0.233 [44.1%]	115	(104.59, 127.42)
	Cmax	0.377 [26.6%]	0.291 [59.8%]	130	(115.55, 145.95)
TreT 48 μg vs. Tyvaso 54 μg	AUC0-5	0.766 [21.8%]	0.757 [42.5%]	101	(91.63, 111.65)
	Cmax	1.07 [28.9%]	0.764 [53.4%]	139	(124.13, 156.73)
TreT 64 μg vs. Tyvaso 72 μg	AUC0-5	0.937 [23.8%]	1.02 [41.9%]	91.5	(83.16, 100.78)
	Cmax	1.27 [28.5%]	1.02 [54.7%]	124	(110.56, 139.61)

TABLE 15

Adverse events for various doses for Tyvaso and TreT administered treprostinil.

	TreT 16 μg N = 34 n (%)	Tyvaso 18 μg N = 34 n (%)	TreT 48 μg N = 34 n (%)	Tyvaso 54 μg N = 34 n (%)	TreT 64 μg N = 33 n (%)	Tyvaso 72 μg N = 35 n (%)
Adverse Events	16 (47.1)	13 (38.2)	23 (67.6)	21 (61.8)	22 (66.7)	25 (71.4)
Cough	15 (44.1)	11 (32.4)	20 (58.8)	18 (52.9)	21 (63.6)	24 (68.6)
Headache	2 (5.9)	3 (8.8)	4 (11.8)	7 (20.6)	6 (18.2)	6 (17.1)
Throat irritation	1 (2.9)	1 (2.9)	3 (8.8)	5 (14.7)	3 (9.1)	4 (11.4)
Dizziness	1 (2.9)	2 (5.9)	1 (2.9)	4 (11.8)	2 (6.1)	2 (5.7)
Nausea	0	0	0	2 (5.9)	2 (6.1)	1 (2.9)
Chest discomfort	1 (2.9)	0	3 (8.8)	2 (5.9)	0	2 (5.7)

Conclusions

AUC0-5 was generally comparable for each TreT and Tyvaso dose level. Cmax values for TreT were slightly higher than Tyvaso Cmax values across dose comparisons. AE profile consistent with known prostacyclin effects and previous studies of Tyvaso. Between-subject variability for both AUC0-5 and Cmax was approximately two-fold less for TreT compared to Tyvaso. AUC0-5 and Cmax for TreT and Tyvaso increased in an approximately dose-proportional manner. Median Tmax: ~10 minutes for TreT and ~10 to 15 minutes with Tyvaso.

Example 5. Aerosolized and Powder Inhaled Treprostinil. Safety Evaluation

Primary Objective

To evaluate the safety and tolerability of Treprostinil Inhalation Powder (TreT) administered by a dry powder inhaler, such as the one shown in FIG. **11**, in subjects with pulmonary arterial hypertension (PAH) currently treated with Tyvaso® (treprostinil inhalation solution administered via a nebulizer)

Secondary Objectives

To evaluate systemic exposure and pharmacokinetics (PK) of treprostinil in subjects with PAH when delivered as Tyvaso® and TreT. To evaluate 6-Minute Walk Distance (6MWD) at study entry and after 3 weeks of treatment with TreT. To evaluate subject satisfaction with and preference for TreT with the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD). To evaluate patient reported PAH symptoms and impact with the PAH-Symptoms and Impact Questionnaire (PAH-SYMPACT).

Eligibility Criteria

Diagnosis of WHO Group I PAH.

Subject must have started Tyvaso≥3 months prior to Baseline and on a stable regimen (no change in dose within 30 days of Baseline Visit) of Tyvaso (6 to 12 breaths QID).

Background therapy for PAH (eg, endothelin receptor antagonist or phosphodiesterase-5-inhibitor or both), on stable dose for a minimum of 30 days prior to Screening. Exclude other prostacyclin analogue or agonist (selexipag, epoprostenol, iloprost, or beraprost).

Excluding subjects with WHO Functional Class IV at Screening.

Subject is not able to perform inhalation maneuvers that meet inspiratory training criteria.

Exclude conditions which limits ambulation or ability to complete 6MWT (Baseline 6MWD>150 m).

Excluded initiation of pulmonary rehabilitation within 12 weeks prior to the Baseline Visit.

FIG. **12** shows a design of the study. Table 16 presents information relating Tret and Tyvaso doses.

TABLE 16

Tyvaso dose (QID)	TreT Dose (QID)	Device usage
6 to 7 breaths	32 μg	32 μg cartridge
8 to 10 breaths	48 μg	48 μg cartridge
11 to 12 breaths	64 μg	32 μg + 32 μg cartridges

TABLE 17

Baseline demographics	
Age (years)	
Median	57.0 (range: 23-82)
Sex, n (%)	
Female	43 (84.3)
Male	8 (15.7)
Current PAH Diagnosis, n (%)	
Idiopathic/familial	29 (56.9)
Associated with unrepaired/repaired congenital shunts	4 (7.8)
Associated with collagen vascular disease	14 (27.5)
Associated with HIV	1 (2.0)
Associated with appetite suppressant/ other drug or toxin use	3 (5.9)
WHO Functional Class at Screening, n (%)	
I	6 (11.8)
II	31 (60.8)
III	14 (27.5)

TABLE 12

Summary of Subject Accountability	TreT Dose in Treatment Phase			
	32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)
Number of Subjects Enrolled	2	27	22	51
Received TreT	2 (100.0)	27 (100.0)	22 (100.0)	51 (100.0)
Enrolled in Optional Extension Phase	2 (100.0)	26 (96.3)	21 (95.5)	49 (96.1)
Subjects Who Discontinued Treatment Phase	0	1 (3.7)	1 (4.5)	2 (3.9)
Adverse Event	0	1 (3.7)	1 (4.5)	2 (3.9)
Subjects Who Discontinued OEP*	0	3 (11.1)	0	3 (5.9)
Adverse Event	0	2 (7.4)	0	2 (3.9)
Lost to Follow-up	0	1 (3.7)	0	1 (2.0)

TABLE 13

Summary of background PAH medication	Overall N = 51; n (%)
ERA	43 (84.3%)
Ambrisentan	24 (47.1%)
Bosentan	2 (3.9%)
Macitentan	17 (33.3%)
PDE5-I	41 (80.4%)
Sildenafil	17 (33.3%)
Tadalafil	24 (47.1%)
sGC	7 (13.7%)
Riociguat	7 (13.7%)

Of the 51 subjects enrolled, assigned TreT doses for 3-week treatment period were 32 μg for 2 subjects; 48 μg for 27 subjects; 64 μg for 22 subjects. 49 subjects rolled into the Optional Extension Phase (OEP). FIG. **13** shows a number of subjects for various maintenance TreT doses in the OEP.

FIG. **14** shows a change in 6 minute walk distance (6MWD) with respect to a baseline 6MWD as a function of duration of TreT treatment. The change from Baseline in 6MWD for TreT overall demonstrated a significant improvement (11.5 m increase; p=0.0217) at Week 3. The improvements in 6MWD for TreT overall were sustained in the Optional Extension Phase.

Patient Reported Outcome Measures

The PQ-ITD is a patient-reported outcome questionnaire to evaluate subject satisfaction with and preference for inhaled treprostinil devices. The PQ-ITD was given at Baseline to evaluate the Tyvaso Inhalation System and at Week 3 to evaluate the TreT Inhaler.

The distribution of responses to each question on the PQ-ITD was significantly improved (p≤0.0003) between Baseline (Tyvaso nebulizer) and Week 3 (TreT inhaler). Overall satisfaction with the TreT inhaler was significantly improved at Week 3 (95.7%, p<0.0001) compared to satisfaction with the Tyvaso nebulizer at Baseline, FIG. **14**.

PAH SYMPACT

The PAH-SYMPACT is a well validated patient-reported outcome questionnaire given to assess PAH symptoms and effects. The PAH-SYMPACT contains four domains (Cardiopulmonary Symptoms, Cardiovascular Symptoms, Physical Impacts, Cognitive/Emotional Impacts) and was given at Baseline, Week 3, and Week 11.

Analysis of patient-reported PAH SYMPACT data revealed a trend of improvement at both Week 3 and Week 11 for subjects receiving TreT.

Mean change from Baseline was lower for all domain scores of the PAH-SYMPACT at both weeks (range: −0.05 to −0.22), with significant improvements for physical impacts (range: −1.1 to 1.0; p=0.0438) and cognitive/emotional impacts (range: −1.3 to 0.5; p=0.0048) at Week 3.

TABLE 18

Overall Safety	TreT Dose in Treatment Phase			
Treatment Phase	32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)
Total number of AEs	0	37	22	59
Total number of SAEs	0	1	1	2
AEs leading to withdrawal of study drug	0	1	1	2
Optional Extension Phase	0			
Total number of AEs	2	51	29	82
Total number of SAEs	0	10	4	14
AEs leading to withdrawal of study drug	0	3	0	3

TABLE 19

Most frequent adverse events during the treatment phase	Treatment Phase Dose				TRIUMPH	
	32 mcg	48 mcg	64 mcg	Overall		
Preferred Term	N = 2 n (%)	N = 27 n (%)	N = 22 n (%)	N = 51 n (%)	Tyvaso n (%)	Placebo n (%)
Cough	0	9 (33.3)	4 (18.2)	13 (25.5)	62 (54)	35 (29)
Headache	0	4 (14.8)	4 (18.2)	8 (15.7)	47 (41)	27 (23)

TABLE 19-continued

Most frequent adverse events during the treatment phase

Preferred Term	Treatment Phase Dose 32 mcg N = 2 n (%)	48 mcg N = 27 n (%)	64 mcg N = 22 n (%)	Overall N = 51 n (%)	TRIUMPH Tyvaso n (%)	Placebo n (%)
Dyspnoea	0	2 (7.4)	1 (4.5)	3 (5.9)	6 (5)	6 (5)
Flushing	0	1 (3.7)	1 (4.5)	2 (3.9)	17 (15)	1 (<1)
Nausea	0	2 (7.4)	0	2 (3.9)	22 (19)	13 (11)
Throat irritation	0	1 (3.7)	1 (4.5)	2 (3.9)	29 (25)*	17 (14)*

*TRIUMPH groups together Throat Irritation and Pharyngolaryngeal Pain.

TABLE 20

Most frequent adverse events during the treatment phase during the optional extension phase

Preferred Term	TreT Dose in Treatment Phase 32 mcg N = 2 n (%)	48 mcg N = 26 n (%)	64 mcg N = 21 n (%)	Overall N = 49 n (%)
Cough	0	3 (11.5)	2 (9.5)	5 (10.2)
Dyspnoea	1 (50.0)	2 (7.7)	2 (9.5)	5 (10.2)
Headache	0	2 (7.7)	2 (9.5)	4 (8.2)
Diarrhoea	0	1 (3.8)	2 (9.5)	3 (6.1)
Pneumonia	0	2 (7.7)	1 (4.8)	3 (6.1)
Arthralgia	0	2 (7.7)	1 (4.8)	3 (6.1)
Dizziness	0	2 (7.7)	1 (4.8)	3 (6.1)

Conclusions

Transition from Tyvaso to TreT was safe and well tolerated in this study. Most adverse effects (AEs) were mild to moderate in severity and occurred at severities and frequencies consistent with those seen in other inhaled treprostinil studies in patients with PAH.

Following 3 weeks of TreT administration, subjects switching from Tyvaso to TreT demonstrated:

Significant improvements in 6MWD (8.0 m increase; p=0.0217) at Week 3. As of 23 Dec. 2020 (data cut-off date), improvements in 6MWD for TreT overall were sustained in the OEP Significant satisfaction with and preference for the use of the TreT inhaler (PQ-ITD) Significant improvement in PAH impact scores, and a trend of improvement in PAH symptom scores (PAH SYMPACT).

Additional Embodiments

1. A method of treating interstitial lung disease (ILD) or pulmonary fibrosis in a subject in need, comprising administering to the subject a therapeutically effective amount of treprostinil, a prodrug, salt, or ester thereof.

2. A method of reducing pulmonary function decline in a subject with interstitial lung disease (ILD) or pulmonary fibrosis, comprising administering to the subject treprostinil, a prodrug, salt, or ester thereof.

3. A method of increasing forced vital capacity (FVC) in a subject suffering from ILD or pulmonary fibrosis, comprising administering to the subject treprostinil, a prodrug, salt, or ester thereof.

4. The method of any one of embodiments 1-3, wherein the ILD comprises one or more of idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), lymphoid interstitial pneumonia (LIP), sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, antisynthetase syndrome, silicosis, asbestosis, occupational lung disease, chronic hypersensitivity pneumonitis, idiopathic interstitial pneumonia (IIP), an autoimmune ILD, lymphangioleiomyomatosis (LAM), Langerhan's cell histiocytosis (LCH), drug associated ILD, vasculitis, granulomatosis, and berylliosis.

5. The method of embodiment 4, wherein the ILD comprises IPF.

6. The method of any one of embodiments 1-5, wherein the ILD comprises systemic sclerosis-associated interstitial lung disease (SSc-ILD).

7. The method of any one of embodiments 1-6, wherein the ILD was induced from antibiotics, chemotherapy, antiarrhythmic agents, coronavirus disease 2019, atypical pneumonia, pneumocystis pneumonia, tuberculosis (TB), *Chlamydia trachomatis*, respiratory syncytial virus, or lymphangitic carcinomatosis.

8. The method of any one of embodiments 1-7, wherein the subject has one or more of surfactant-protein-B deficiency, surfactant-protein-C deficiency, ABCA3-deficiency, brain lung thyroid syndrome, congenital pulmonary alveolar proteinosis, alveolar capillary dysplasia, mutations in telomerase reverse transcriptase, mutations in telomerase RNA component, mutations in the regulator of telomere elongation helicase 1, and mutations in poly(A)-specific ribonuclease.

9. The method of any one of embodiments 1-8, wherein the subject has one or more symptoms of shortness of breath, fatigue, weight loss, dry cough, chest pain, and lung hemorrhage.

10. The method of embodiment 9, wherein after administration the symptom is improved by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as measured by a medically-recognized technique.

11. The method of embodiment 10, wherein the medically-recognized technique comprises one or more of Modified Medical Research Council (MMRC) Dyspnoea Scale, Modified Borg Dyspnoea Scale (0-10), Chalder Fatigue Scale, weight measurement scale, visual analogue scale (VAS) for cough, King's Brief Interstitial Lung Disease Questionnaire, Leicester Cough Questionnaire (LCQ), computed tomography (CT) scan, X-ray, multiple magnetic

resonance imaging (MRI), pulmonary function testing (PFT), spirometry, lung volumes, maximal respiratory pressure, diffusing capacity, oxygen desaturation, and arterial blood gas evaluation.

12. The method of any one of embodiments 1-11, wherein treprostinil, a prodrug, salt, or ester thereof is administered in a pharmaceutical composition comprising treprostinil, a prodrug, salt, or ester thereof and a pharmaceutically acceptable carrier or excipient.

13. The method of claim any one of embodiments 1-12, wherein the administration comprises at least one of oral, inhalation, subcutaneous, nasal, intravenous, intramuscular, sublingual, buccal, rectal, vaginal, and transdermal administration.

14. The method of any one of embodiments 1-13, wherein the administration comprises inhalation.

15. The method of any one of embodiments 1-14, wherein a single inhalation administration event comprises from 1 to 20 breaths.

16. The method of any one of embodiments 1-15, comprising administration of at least one additional active agent to treat the IRD.

17. The method of embodiment 16, wherein the at least one additional active agent comprises a corticosteroid, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, pirfenidone, or nintedanib.

18. The method of embodiment 16 or 17, wherein the at least one additional active agent and treprostinil, a prodrug, salt, or ester thereof, are administered via a method selected from the group consisting of

(a) concomitantly;

(b) as an admixture;

(c) separately and simultaneously or concurrently; and

(d) separately and sequentially.

19. The method of any one of embodiments 1-18, wherein administration is once, twice, thrice, four times, five times, or six times per day.

20. The method of any one of embodiments 1-19, wherein administration is for a period selected from the group consisting of about 1 day, about 1 day to about 3 days, about 3 days to about 6 days, about 6 days to about 9 days, about 9 days to about 12 days, about 12 days to about 15 days, about 15 days to about 18 days, about 18 days to about 21 days, about 21 days to about 24 days, about 24 days to about 27 days, about 27 days to about 30 days, or about greater than 30 days.

21. The method of any one of embodiments 1-20, wherein the subject is a human.

22. The method of any one of embodiments 1-21, wherein the method results in an increased FVC compared to the FVC at the start of or prior to the start of administration.

23. The method of embodiment 22, wherein the administration results in an increased FVC at sixteen weeks after the start of administration compared to the FVC at the start of or prior to the start of administration.

24. The method of any one of embodiments 22-23, wherein the increase in FVC is at least 20%.

25. The method of embodiment 24, wherein the increase is FVC is at least 75%.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.

2. The method of claim **1**, wherein said administering provides a statistically significant increase of a 6 minutes walk distance in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

3. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks, 12 weeks, or 16 weeks of the administering.

4. The method of claim **1**, wherein said administering provides a statistically significant reduction of a plasma concentration of NT-proBNP in the patient after 8 weeks, 12 weeks, or 16 weeks of the administering.

5. The method of claim **1**, wherein said administering reduces a plasma concentration of NT-proBNP in the patient by at least 200 pg/ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

6. The method of claim **1**, wherein said administering provides a statistically significant reduction of at least one exacerbations of the interstitial lung disease.

7. The method of claim **1**, wherein said administering provides a statistically significant reduction of clinical worsening events due to the interstitial lung disease.

8. The method of claim **7**, wherein the clinical worsening events comprise at least one of hospitalization for cardiopulmonary indication and a decrease in a 6-minute walk distance by more than 15% compared a baseline 6-minute walk distance prior to the administering.

9. The method of claim **1**, wherein said administering provides a statistically significant improves of forced vital capacity (FVC) in the patient after 8 weeks, 12, weeks or 16 weeks of the administering.

10. The method of claim **9**, wherein said administering improves the forced vital capacity (FVC) in the patient by at least 20 ml after 8 weeks, 12 weeks, or 16 weeks of the administering.

11. The method of claim **1**, wherein said administering is performed by a pulsed inhalation device.

12. The method of claim **11**, wherein the pulsed inhalation device contains an inhalation solution comprising treprostinil or a pharmaceutically acceptable salt thereof.

13. The method of claim **11**, wherein the pulsed inhalation device is a nebulizer.

14. The method of claim **11**, wherein the pulsed inhalation device is a dry powder inhaler comprising a dry powder comprising treprostinil or a pharmaceutically acceptable salt thereof.

15. The method of claim **1**, wherein the effective amount of treprostinil or a pharmaceutically acceptable salt administered to the patient in a single inhalation administration event is from 15 μg to 100 μg.

16. The method of claim **15**, wherein the single inhalation administration event does not exceed 15 breaths by the patient.

17. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 10 m after 8 weeks of the administering.

18. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 12 weeks of the administering.

19. The method of claim **1**, wherein said administering increases a 6 minutes walk distance of the patient by at least 15 m after 16 weeks of the administering.

* * * * *

EXHIBIT 7

US010716793B2

(12) United States Patent
Olschewski et al.

(10) **Patent No.: US 10,716,793 B2**
(45) **Date of Patent: *Jul. 21, 2020**

(54) **TREPROSTINIL ADMINISTRATION BY INHALATION**

(71) Applicant: **United Therapeutics Corporation**, Silver Spring, MD (US)

(72) Inventors: **Horst Olschewski**, Graz (AT); **Robert Roscigno**, Chapel Hill, NC (US); **Lewis J. Rubin**, LaJolla, CA (US); **Thomas Schmehl**, Giessen (DE); **Werner Seeger**, Giessen (DE); **Carl Sterritt**, Weybridge (GB); **Robert Voswinckel**, Giessen (DE)

(73) Assignee: **United Therapeutics Corporation**, Silver Spring, MD (US)

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This patent is subject to a terminal disclaimer.

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(60) Continuation of application No. 16/536,954, filed on Aug. 9, 2019, which is a continuation of application No. 15/011,999, filed on Feb. 1, 2016, now Pat. No. 10,376,525, which is a division of application No. 13/469,854, filed on May 11, 2012, now Pat. No. 9,339,507, which is a division of application No. 12/591,200, filed on Nov. 12, 2009, now Pat. No. 9,358,240, which is a continuation of application No. 11/748,205, filed on May 14, 2007, now abandoned.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Jeffrey S Lundgren
Assistant Examiner — Michael J Schmitt
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

8 Claims, 12 Drawing Sheets

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Watson Laboratories, Inc. (Petitioner) v. *United Therapeutics Corp.* (Patent Owner), Petition for Inter Partes Review, IRP2017-01621, U.S. Pat. No. 9,358,240, with only Exhibits 1002, 1059, 1161 and 1164 and not including exhibits already provide with C2.

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FIGURE 1

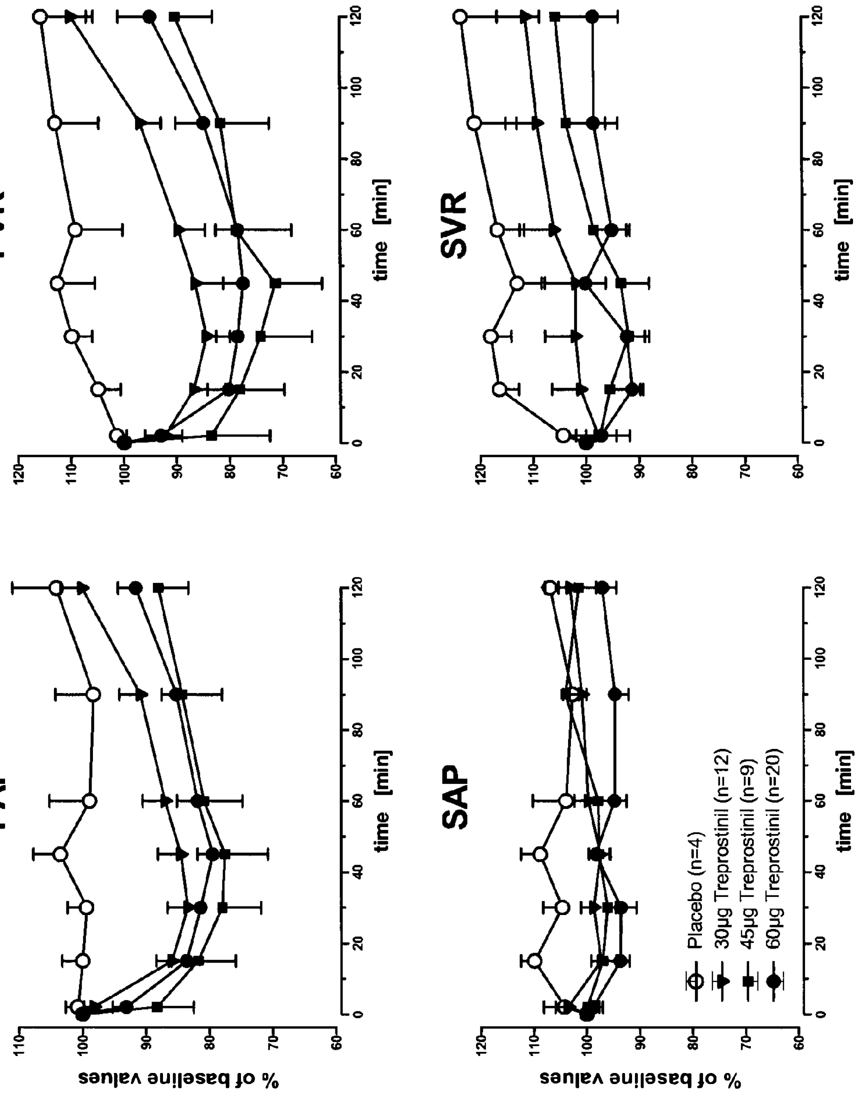

PAP
PVR
SAP
SVR
% of baseline values
% of baseline values
time [min]
time [min]
time [min]
time [min]
Placebo (n=4)
30µg Treprostinil (n=12)
45µg Treprostinil (n=9)
60µg Treprostinil (n=20)

FIGURE 2

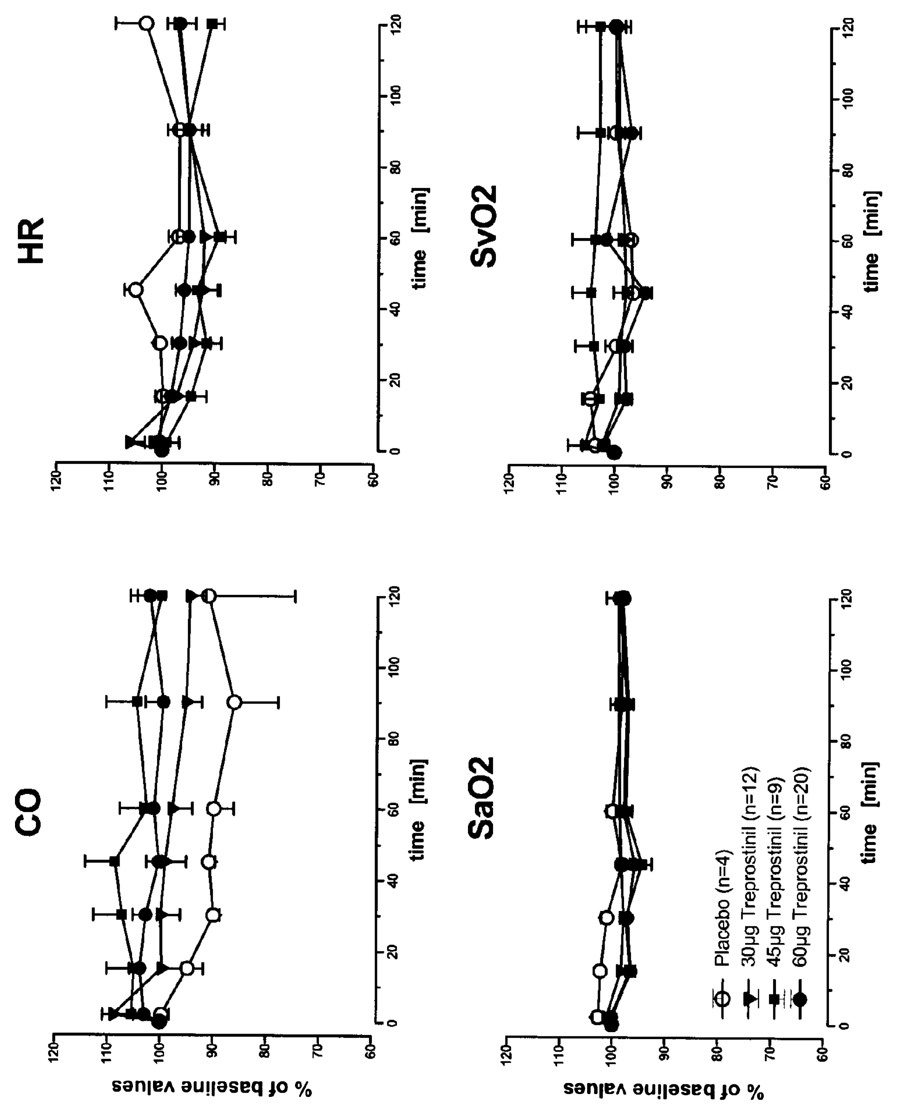

CO
HR
SaO2
SvO2
% of baseline values
time [min]
Placebo (n=4)
30μg Treprostinil (n=12)
45μg Treprostinil (n=9)
60μg Treprostinil (n=20)

FIGURE 3

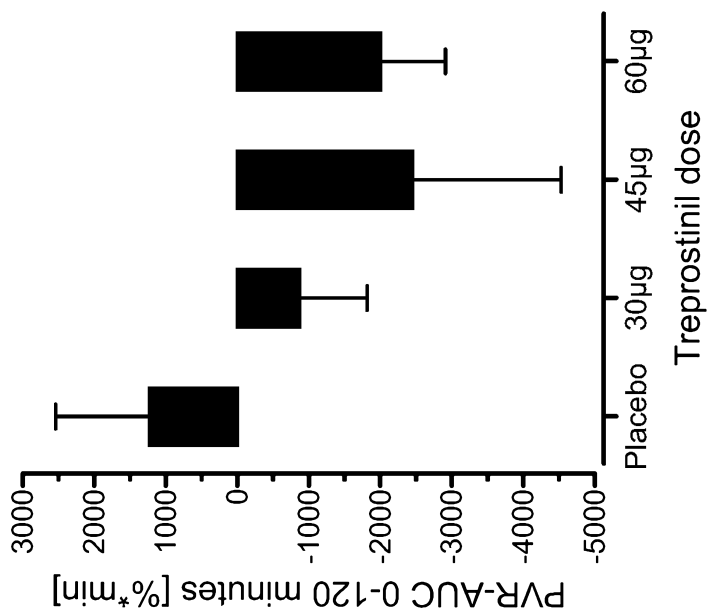

PVR-AUC 0-120 minutes [%*min]
3000
2000
1000
0
-1000
-2000
-3000
-4000
-5000
Placebo
30µg
45µg
60µg
Treprostinil dose

FIGURE 4

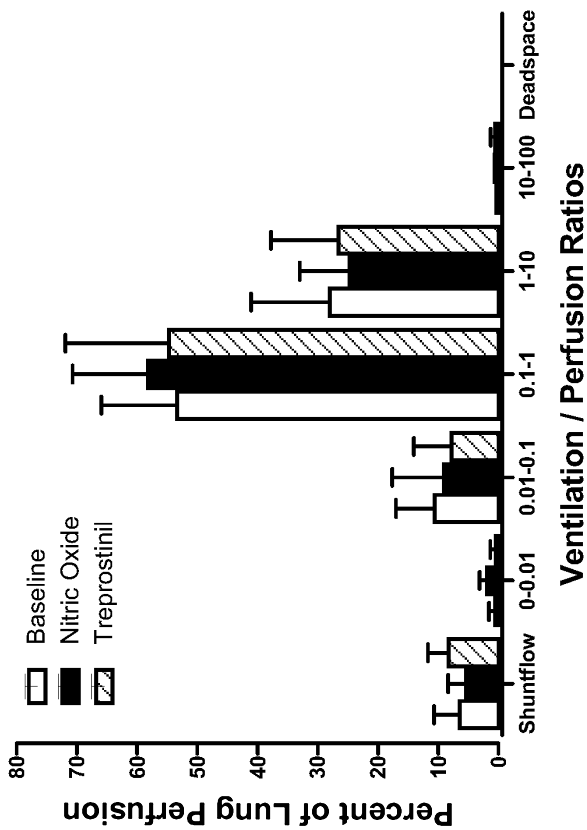

Baseline
Nitric Oxide
Treprostinil
Percent of Lung Perfusion
80
70
60
50
40
30
20
10
0
Shuntflow
0-0.01
0.01-0.1
0.1-1
1-10
10-100
Deadspace
Ventilation / Perfusion Ratios

FIGURE 5

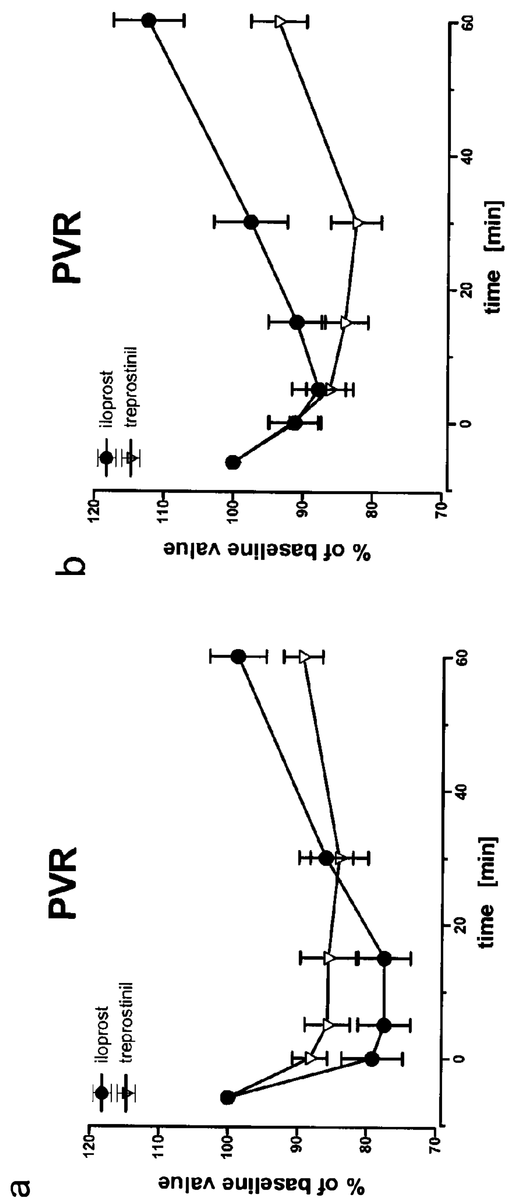

a
PVR
iloprost
treprostinil
% of baseline value
time [min]
b
PVR
iloprost
treprostinil
% of baseline value
time [min]

FIGURE 6

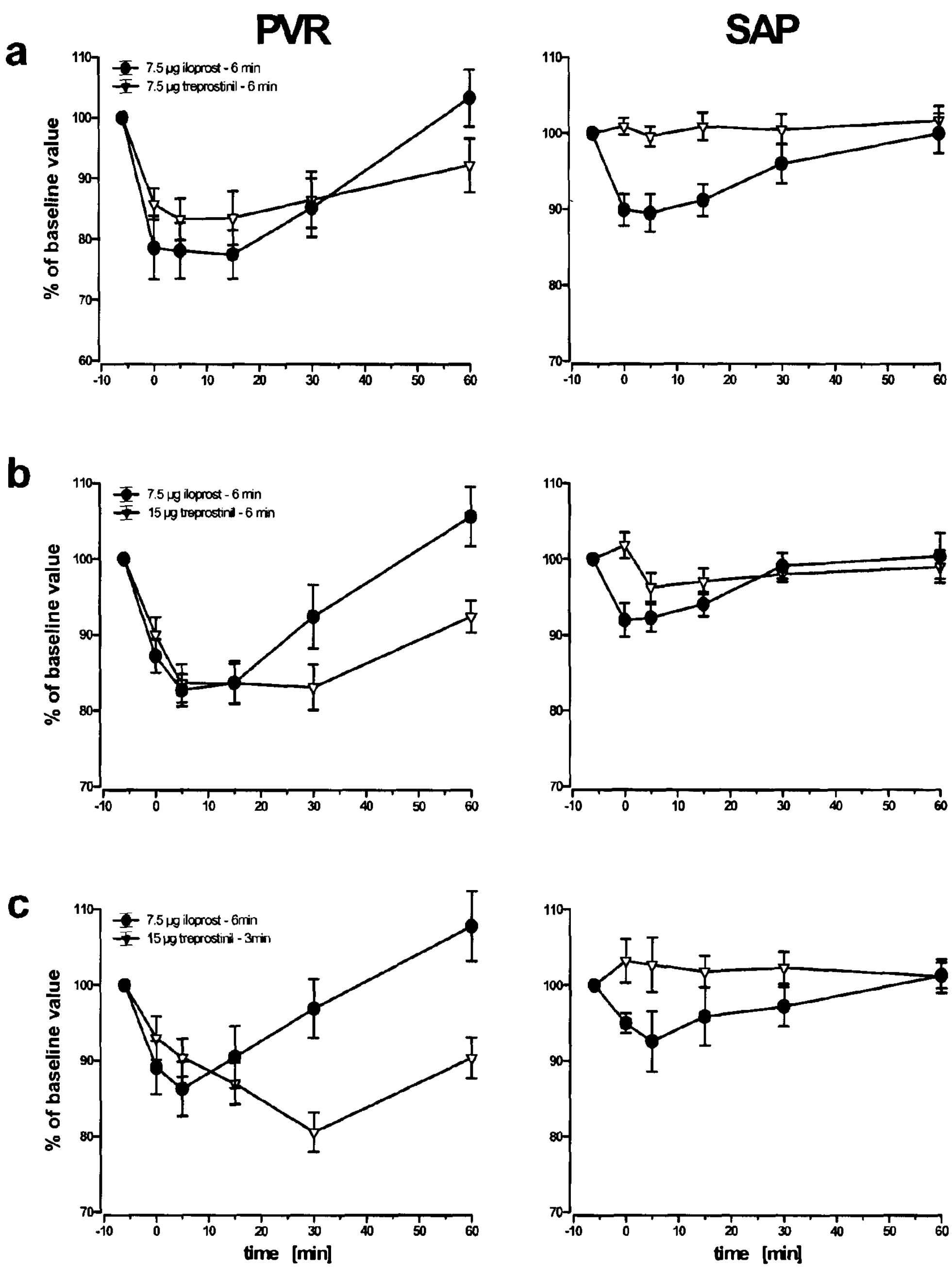
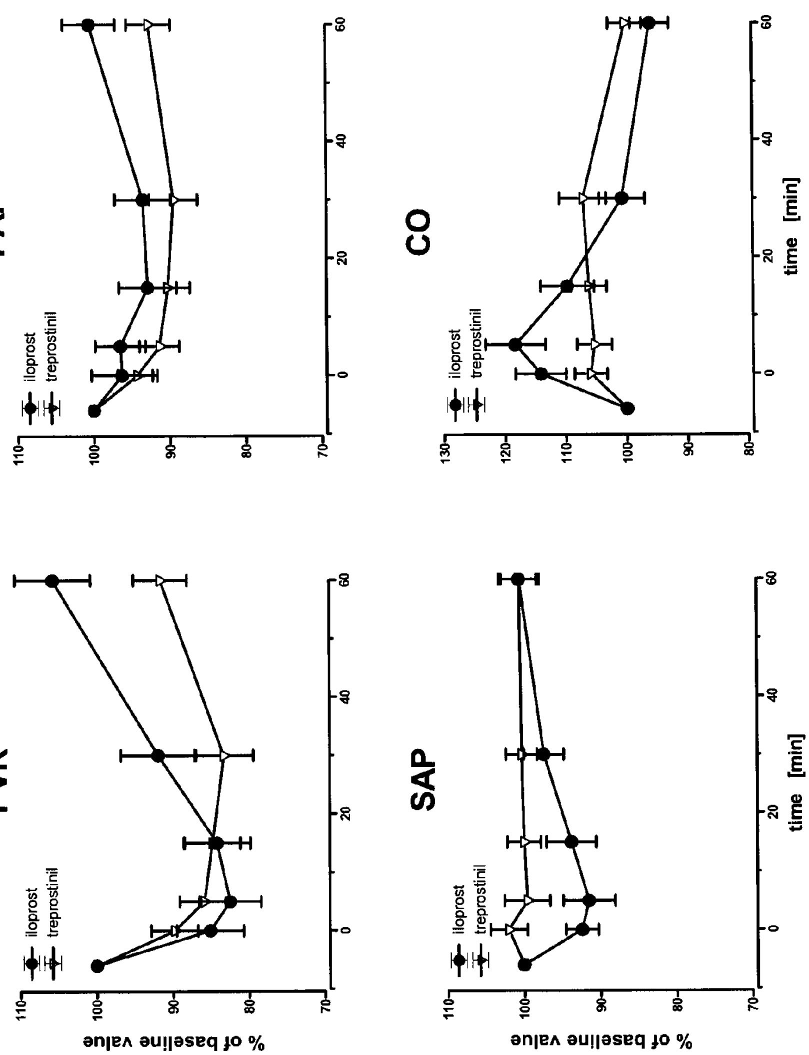

PVR
SAP
a
7.5 µg iloprost - 6 min
7.5 µg treprostinil - 6 min
b
7.5 µg iloprost - 6 min
15 µg treprostinil - 6 min
c
7.5 µg iloprost - 6min
15 µg treprostinil - 3min
% of baseline value
time [min]

FIGURE 7



PVR
PAP
SAP
CO
iloprost
treprostinil
% of baseline value
time [min]

FIGURE 8

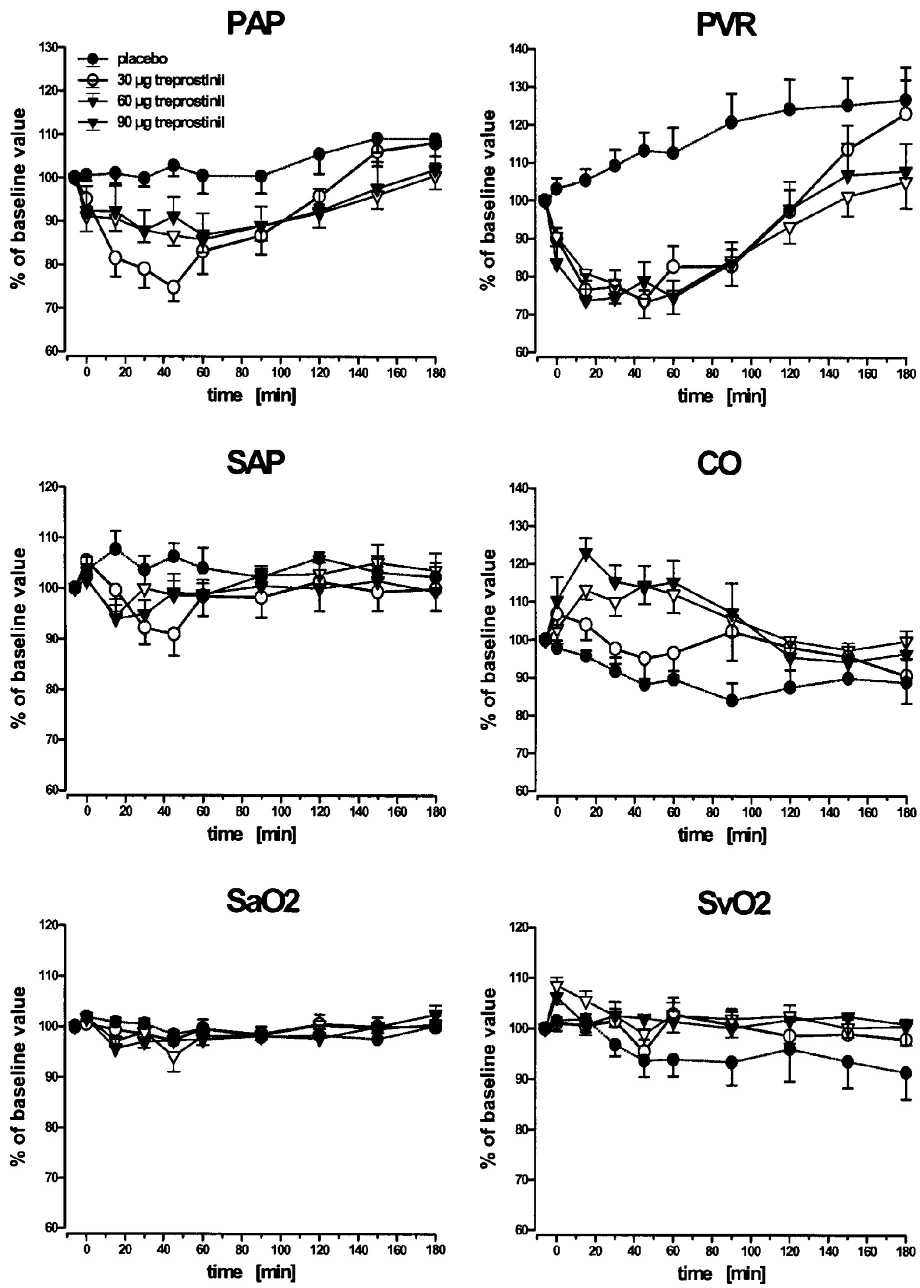

PAP
placebo
30 µg treprostinil
60 µg treprostinil
90 µg treprostinil
% of baseline value
time [min]
PVR
SAP
CO
SaO2
SvO2

FIGURE 9

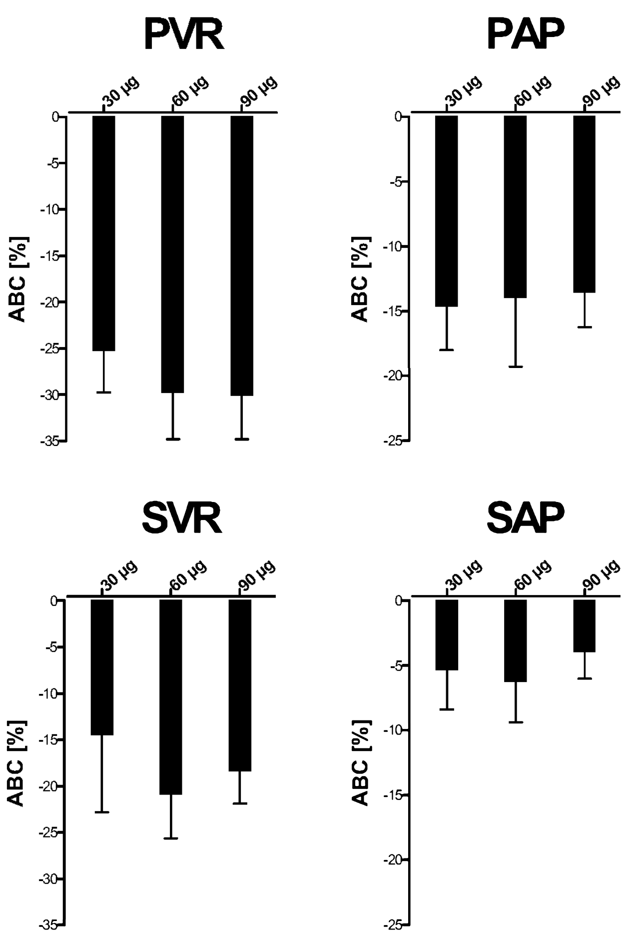


FIGURE 10

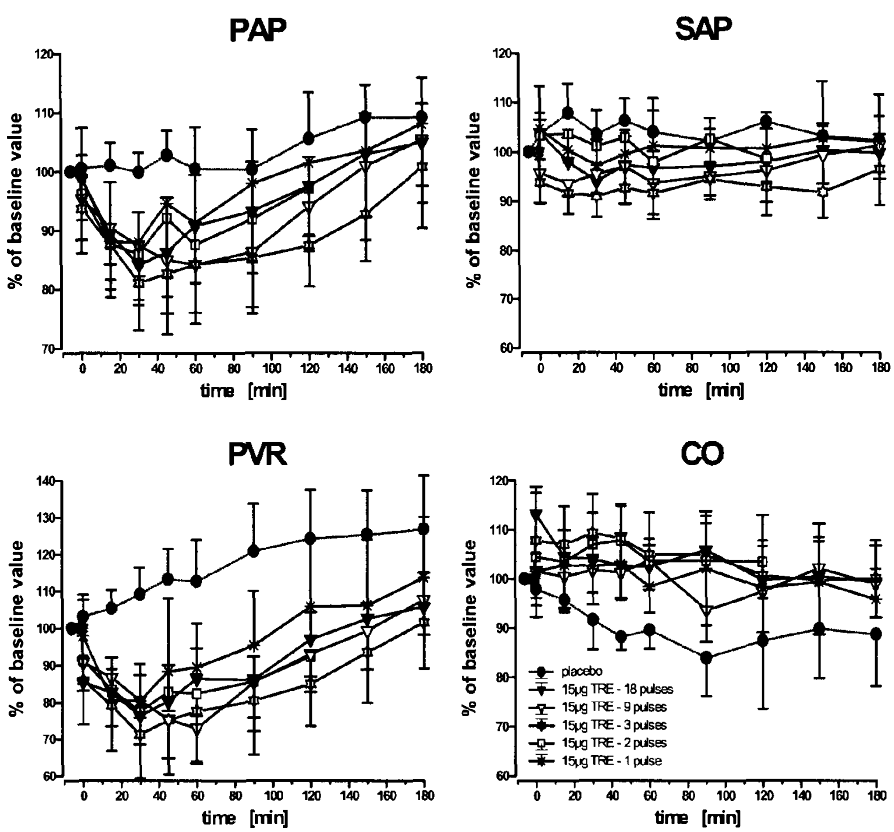

PAP
SAP
PVR
CO
% of baseline value
time [min]
placebo
15µg TRE - 18 pulses
15µg TRE - 9 pulses
15µg TRE - 3 pulses
15µg TRE - 2 pulses
15µg TRE - 1 pulse

FIGURE 11

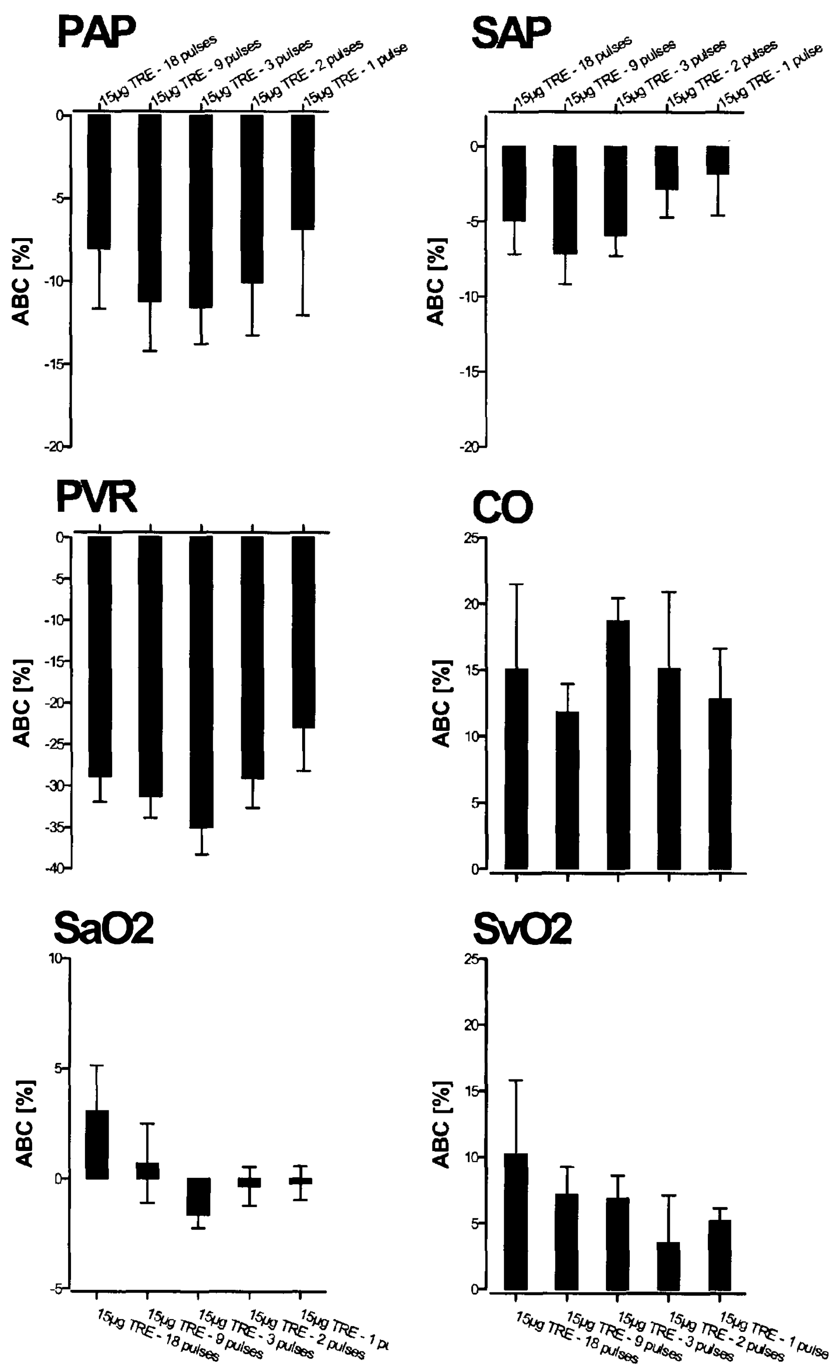
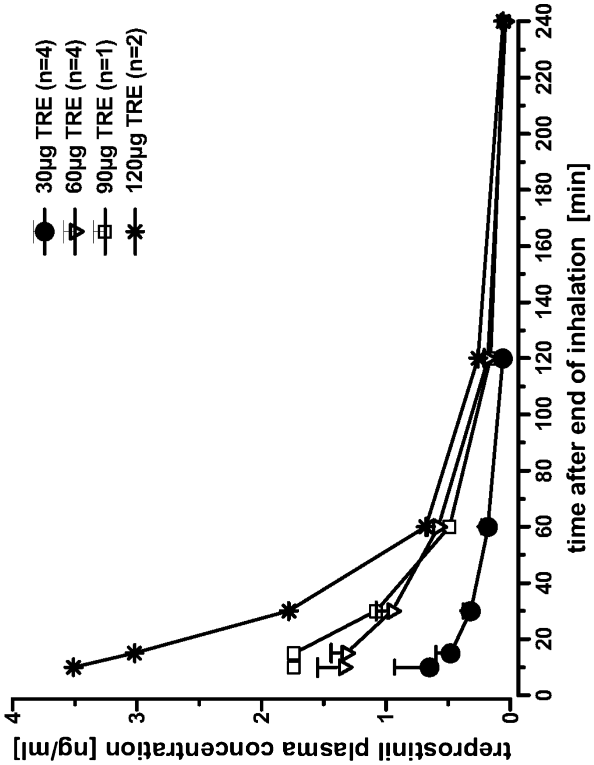

PAP
SAP
PVR
CO
SaO2
SvO2
ABC [%]
15µg TRE - 18 pulses
15µg TRE - 9 pulses
15µg TRE - 3 pulses
15µg TRE - 2 pulses
15µg TRE - 1 pulse

FIGURE 12


30µg TRE (n=4)
60µg TRE (n=4)
90µg TRE (n=1)
120µg TRE (n=2)
treprostinil plasma concentration [ng/ml]
time after end of inhalation [min]
0
1
2
3
4
0
20
40
60
80
100
120
140
160
180
200
220
240

TREPROSTINIL ADMINISTRATION BY INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation of U.S. application Ser. No. 16/536,954, filed Aug. 9, 2019, which is a Continuation of U.S. application Ser. No. 15/011,999, filed Feb. 1, 2016, which is a Divisional of U.S. application Ser. No. 13/469,854, filed May 11, 2012, Divisional of U.S. application Ser. No. 12/591,200, filed Nov. 12, 2009, which is a Continuation of U.S. application Ser. No. 11/748,205, filed May 14, 2007, which claims priority to U.S. provisional application No. 60/800,016 filed May 15, 2006, which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The present application relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits.

BACKGROUND OF THE INVENTION

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. The above described condition is referred to as pulmonary hypertension (PH). Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention, see e.g. Simonneau G., et al. J. Am. Coll. Cardiol. 2004; 43(12 Suppl S):5S-12S. Pulmonary hypertension can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. In addition, certain infectious diseases, such as HIV and liver diseases with portal hypertension may cause pulmonary hypertension. Autoimmune disorders, such as collagen vascular diseases, also often lead to pulmonary vascular narrowing and contribute to a significant number of pulmonary hypertension patients. The cases of pulmonary hypertension remain where the cause of the increased resistance is as yet inexplicable are defined as idiopathic (primary) pulmonary hypertension (iPAH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension and are in the majority of cases related to a genetic mutation in the bone morphogenetic protein receptor-2 gene. The cases of idiopathic

pulmonary arterial hypertension tend to comprise a recognizable entity of about 40% of patients cared for in large specialized pulmonary hypertension centers. Approximately 65% of the most commonly afflicted are female and young adults, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short without specific treatment, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, disease progress is inexorable via syncope and right heart failure and death is quite often sudden.

Pulmonary hypertension refers to a condition associated with an elevation of pulmonary arterial pressure (PAP) over normal levels. In humans, a typical mean PAP is approximately 12-15 mm Hg. Pulmonary hypertension, on the other hand, can be defined as mean PAP above 25 mmHg, assessed by right heart catheter measurement. Pulmonary arterial pressure may reach systemic pressure levels or even exceed these in severe forms of pulmonary hypertension. When the PAP markedly increases due to pulmonary venous congestion, i.e. in left heart failure or valve dysfunction, plasma can escape from the capillaries into the lung interstitium and alveoli. Fluid buildup in the lung (pulmonary edema) can result, with an associated decrease in lung function that can in some cases be fatal. Pulmonary edema, however, is not a feature of even severe pulmonary hypertension due to pulmonary vascular changes in all other entities of this disease.

Pulmonary hypertension may either be acute or chronic. Acute pulmonary hypertension is often a potentially reversible phenomenon generally attributable to constriction of the smooth muscle of the pulmonary blood vessels, which may be triggered by such conditions as hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism. Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature, which result in a decreased cross-sectional area of the pulmonary blood vessels. This may be caused by, for example, chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes as in idiopathic pulmonary arterial hypertension.

Pulmonary hypertension has been implicated in several life-threatening clinical conditions, such as adult respiratory distress syndrome ("ARDS") and persistent pulmonary hypertension of the newborn ("PPHN"). Zapol et al., Acute Respiratory Failure, p. 241-273, Marcel Dekker, New York (1985); Peckham, J. Ped. 93:1005 (1978). PPHN, a disorder that primarily affects full-term infants, is characterized by elevated pulmonary vascular resistance, pulmonary arterial hypertension, and right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale of the newborn's heart. Mortality rates range from 12-50%. Fox, Pediatrics 59:205 (1977); Dworetz, Pediatrics 84:1 (1989). Pulmonary hypertension may also ultimately result in a potentially fatal heart condition known as "cor pulmonale," or pulmonary heart disease. Fishman, "Pulmonary Diseases and Disorders" 2nd Ed., McGraw-Hill, New York (1988).

Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device, such as a metered dose inhaler.

SUMMARY OF THE INVENTION

One embodiment is a method of delivering to a subject in need thereof a therapeutically effective amount of trepros-

tinil, or treprostinil derivative or a pharmaceutically acceptable salt thereof comprising administering to the subject a therapeutically effective amount of the treprostinil or treprostinil derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Another embodiment is a method for treating pulmonary hypertension comprising administering to a subject in need thereof treprostinil or its derivative, or a pharmaceutically acceptable salt thereof using a metered dose inhaler.

Yet another embodiment is a kit comprising a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or treprostinil derivative, or a pharmaceutically acceptable salt thereof.

And yet another embodiment is a kit for treating pulmonary hypertension in a subject, comprising (i) an effective amount of treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; (ii) a metered dose inhaler; (iii) instructions for use in treating pulmonary hypertension.

Administration of treprostinil using a metered dose inhaler can provide patients, such as pulmonary hypertension patients, with a high degree of autonomy.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** pulmonary and systemic changes in hemodynamics following the inhalation of placebo (open circles), 30 μg treprostinil (triangles), 45 μg treprostinil (squares) or 60 μg TREprostinil (black circles) applied by a Metered Dose Inhaler (MDI-TRE). A single short inhalation of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60 μg MDI-TRE. Systemic arterial pressure and resistance were not significantly affected. PAP=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; SAP=mean systemic arterial pressure; SVR=systemic vascular resistance. Data are given as mean value±standard error of the mean (SEM).

FIG. **2** presents hemodynamic changes induced by the inhalation of placebo (open circles), 30 μg treprostinil (triangles), 45 μg treprostinil (squares) or 60 μg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. CO=cardiac output; HR=heart rate; SaO2=arterial oxygen saturation; SvO2=central venous oxygen saturation. Data are given as mean value±SEM.

FIG. 3 shows areas under the curve for changes in pulmonary vascular resistance (PVR) calculated for an observation period of 120 minutes after inhalation treprostinil using a metered dose inhaler. PVR was markedly lowered by treprostinil inhalation. The increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean value±95% confidence intervals.

FIG. **4** demonstrates Ventilation-perfusion matching measured with the multiple inert gas elimination technique. Five patients (30 μg TRE, n=2; 45 μg TRE, n=1; 60 μg TRE, n=2) with pre-existing gas exchange problems were investigated for changes in ventilation-perfusion ratios. All patients had significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation using a metered dose inhaler (MDI-TRE). MDI-TRE applied at high treprostinil concentrations did not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean value±95% confidence intervals.

FIG. **5** presents response of pulmonary vascular resistance (PVR) to inhaled treprostinil vs. iloprost—period effects. a) First inhalation with treprostinil (n=22) vs. first inhalation with iloprost (n=22); b) second inhalation with treprostinil (n=22) vs. second inhalation with iloprost (n=22). The PVR decrease with treprostinil was delayed and prolonged, compared to iloprost. Due to carryover effects from the first period, in the second period, the effects of both drugs appeared shortened. Data are shown as percent of baseline values (mean value±95% confidence interval).

FIG. **6** presents response of PVR and systemic arterial pressure (SAP) to inhalation of treprostinil vs. iloprost—dose effects. a) Inhalation of 7.5 μg iloprost (in 6 min) vs. 7.5 μg treprostinil (6 min) (n=14, in a randomized order). b) Inhalation of 7.5 μg iloprost (6 min) vs. 15 μg treprostinil (6 min) (n=14, in randomized order). c) Inhalation of 7.5 μg iloprost (6 min) vs. 15 μg treprostinil (3 min) (n=16, in randomized order). Data are shown as percent of baseline values (mean±95% confidence interval). Iloprost, filled circles; Treprostinil, open triangles.

FIG. **7** presents hemodynamic response to inhalation of treprostinil vs. iloprost. Data from n=44 patients, who inhaled both drugs in randomized order, shown as percent of baseline values (mean value±95% confidence interval). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. **8** presents pharmacodynamics after treprostinil inhalation vs. placebo. Placebo or treprostinil in doses of 30 μg, 60 μg or 90 μg were inhaled (means±95% confidence intervals). Maximal decrease of PVR was comparable for all doses. The duration of pulmonary vasodilation (PVR-decrease) appeared to be dose dependent. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output; SaO2, arterial oxygen saturation; SvO2, mixed venous oxygen saturation.

FIG. **9** presents Areas Between the placebo and the treprostinil Curves (ABC). ABCs were calculated for a 3-hour period after inhalation of TRE or placebo from the relative changes of hemodynamic parameters (means±95% confidence intervals). PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance.

FIG. **10** presents hemodynamic responses to the inhalation of 15 μg treprostinil. The inhalation time by increasing treprostinil concentration. A pulse of aerosol was generated every 6 seconds. TRE aerosol was inhaled in concentrations of 100 μg/ml (18 pulses; n=6), 200 μg/ml (9 pulses; n=6), 600 μg/ml (3 pulses; n=21), 1000 μg/ml (2 pulses; n=7) and 2000 μg/ml (1 pulse; n=8). Placebo data correspond to FIG. **8**. Data are shown as means±95% confidence intervals. PVR, pulmonary vascular resistance; PAP, mean pulmonary arterial pressure; SAP, mean systemic arterial pressure; CO, cardiac output.

FIG. **11** presents areas between the placebo curve and the responses to 15 μg treprostinil applied at increasing concentrations to minimize inhalation time. Mean±SEM of relative changes of hemodynamic parameters (observation time 120 min). PAP, pulmonary arterial pressure, SAP, systemic arterial pressure, PVR, pulmonary vascular resistance, CO, cardiac output, SaO2, systemic arterial oxygen saturation, SvO2, pulmonary arterial oxygen saturation.

FIG. **12** presents pharmacokinetics of treprostinil after a single inhalation. Treprostinil plasma levels after inhalation of 30 μg, 60 μg, 90 μg or 120 μg treprostinil (6 min

inhalation period; experiments correspond to those shown in FIGS. **8** and **9**). Data with error bars represent mean values±SEM.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise specified, the term "a" or "an" used herein shall mean "one or more."

The present application incorporates herein by reference in its entirety Voswinckel R, et al. J. Am. Coll. Cardiol. 2006; 48:1672-1681.

The inventors discovered that a therapeutically effective dose of treprostinil can be administered in a few single inhalations using a compact inhalation device, such as a metered dose inhaler. Furthermore, the inventors discovered that such administering does not cause significant side effects, especially no significant side effects related to systemic blood pressure and circulation as well as no gas exchange deteriorations or disruptions.

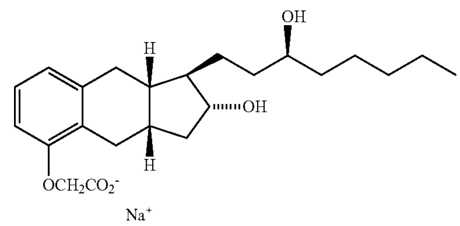
Accordingly, one embodiment of the invention is a method of delivering to a subject in need thereof, such as a human being, a therapeutically effective amount of treprostinil comprising administering to the subject a formulation comprising a therapeutically effective amount of treprostinil, its derivative or a pharmaceutically acceptable salt thereof using a metered dose inhaler. Treprostinil can be administered via a metered dose inhaler to a subject affected with a condition or disease, which can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

Another embodiment of the invention is a method for treating pulmonary hypertension, comprising administering to a subject in need thereof, such as a human being, treprostinil or its derivative, or a pharmaceutically acceptable salt using a metered dose inhaler.

Treprostinil, or 9-deoxy-2',9-alpha-methano-3-oxa-4,5,6-trinor-3,7-(1'3'-interphenylene)-13,14-dihydro-prostaglandin F1, is a prostacyclin analogue, first described in U.S. Pat. No. 4,306,075. U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. US patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. US patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. provisional application No. 60/900,320 filed Feb. 9, 2007, discloses treprostinil treatment of pulmonary fibrosis.

The term "acid derivative" is used herein to describe C1-4 alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C1-4 alkyl groups.

The present invention also encompasses methods of using Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof. In one embodiment, a method uses Treprostinil sodium, currently marketed under the trade name of REMODULIN®. The FDA has approved Treprostinil sodium for the treatment of pulmonary arterial hypertension by injection of dose concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. The chemical structure formula for Treprostinil sodium is:



Treprostinil sodium is sometimes designated by the chemical names: (a) [(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid; or (b) 9-deoxy-2',9-α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F_1. Treprostinil sodium is also known as: UT-15; LRX-15; 15AU81; UNIPROST™; BW A15AU; and U-62,840. The molecular weight of Treprostinil sodium is 390.52, and its empirical formula is $C_{23}H_{34}O_5$.

In certain embodiments, treprostinil can be administered in combination with one or more additional active agents. In some embodiments, such one or more additional active agents can be also administered together with treprostinil using a metered dose inhaler. Yet in some embodiments, such one or more additional active agents can be administered separately from treprostinil. Particular additional active agents that can be administered in combination with treprostinil may depend on a particular disease or condition for treatment or prevention of which treprostinil is administered. In some cases, the additional active agent can be a cardiovascular agent such as a calcium channel blocker, a phosphodiesterase inhibitor, an endothelial antagonist, or an antiplatelet agent.

The present invention extends to methods of using physiologically acceptable salts of Treprostinil, as well as non-physiologically acceptable salts of Treprostinil that may be used in the preparation of the pharmacologically active compounds of the invention.

The term "pharmaceutically acceptable salt" refers to a salt of Treprostinil with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Salts of inorganic bases can be, for example, salts of alkali metals such as sodium or potassium; alkaline earth metals such as calcium and magnesium or aluminum; and ammonia. Salts of organic bases can be, for example, salts trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, and triethanolamine. Salts of inorganic acids can be, for example, salts of hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Salts of organic acids can be, for example, salts of formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, lactic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Salts of basic amino acids can be, for example, salts of arginine, lysine and ornithine. Salts of acidic amino acids can include, for example, salts of aspartic acid and glutamic acid. Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sul-

phates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

Preferred pharmaceutically acceptable salts are disclosed, for example, in US patent application publication No. 20050085540.

Treprostinil can be administered by inhalation, which in the present context refers to the delivery of the active ingredient or a combination of active ingredients through a respiratory passage, wherein the subject in need of the active ingredient(s) through the subject's airways, such as the subject's nose or mouth.

A metered dose inhaler in the present context means a device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs. One example of the inhalation device can be a pressurized metered dose inhaler, a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.

The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

The metered dose inhaler can be a soft mist inhaler (SMI), in which the aerosol cloud containing a respiratory drug can be generated by passing a solution containing the respiratory drug through a nozzle or series of nozzles. The aerosol generation can be achieved in SMI, for example, by mechanical, electromechanical or thermomechanical process. Examples of soft mist inhalers include the Respimat® Inhaler (Boeringer Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated). For a review of soft mist inhaler technology, see e.g. M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34. The aerosol for SMI can be generated from a solution of the respiratory drug further containing pharmaceutically acceptable excipients. In the present case, the respiratory drug is treprostinil, its derivative or a pharmaceutically acceptable salt thereof, which can be formulated in SMI is as a solution. The solution can be, for example, a solution of treprostinil in water, ethanol or a mixture thereof. Preferably, the diameter of the treprostinil-containing aerosol particles is less than about 10 microns, or less than about 5 microns, or less than about 4 microns.

Treprostinil concentration in an aerosolable formulation, such as a solution, used in a metered dose inhaler can range from about 500 μg/ml to about 2500 μg/ml, or from about 800 μg/ml to about 2200 μg/ml, or from about 1000 μg/ml to about 2000 μg/ml.

The dose of treprostinil that can be administered using a metered dose inhaler in a single event can be from about 15 μg to about 100 μg or from about 15 μg to about 90 μg or from about 30 μg to about 90 μg or from about 30 μg to about 60 μg.

Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient. For example, treprostinil can be administered in 20 breaths or less, or in 10 breaths or less, or than 5 breaths or less. Preferably, treprostinil is administered in 3, 2 or 1 breaths.

The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.

Treprostinil can be administered a single time per day or several times per day.

In some embodiments, the method of treatment of pulmonary hypertension can further comprise administering at least one supplementary agent selected from the group consisting of sildenafil, tadalafil, calcium channel blockers (diltiazem, amlodipine, nifedipine), bosentan, sitaxsentan, ambrisentan, and pharmaceutically acceptable salts thereof. In some embodiments, the supplementary agents can be included in the treprostinil formulation and, thus, can be administered simultaneously with treprostinil using a metered dose inhaler. In some embodiments, the supplementary agents can be administered separately from treprostinil. In some embodiments, the application of intravenous prostacyclin (flolan), intravenous iloprost or intravenous or subcutaneous treprostinil can be administered in addition to treprostinil administered via inhalation using a metered dose inhaler.

The present invention also provides a kit that includes a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof. Such a kit can further include instructions on how to use the metered dose inhaler for inhaling treprostinil. Such instructions can include, for example, information on how to coordinate patient's breathing, and actuation of the inhaler. The kit can be used by a subject, such as human being, affected with a disease or condition that can be treated by treprostinil, such as asthma, pulmonary hypertension, peripheral vascular disease or pulmonary fibrosis.

In some cases, the kit is a kit for treating pulmonary hypertension, that includes (i) a metered dose inhaler containing a pharmaceutical formulation comprising treprostinil or its derivative, or a pharmaceutically acceptable salt thereof; and (ii) instructions for use of the metered dose inhaler containing treprostinil in treating pulmonary hypertension.

As used herein, the phrase "instructions for use" shall mean any FDA-mandated labeling, instructions, or package inserts that relate to the administration of Treprostinil or its derivatives, or pharmaceutically acceptable salts thereof, for treatment of pulmonary hypertension by inhalation. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms associated with pulmonary hypertension, that can be ameliorated by Treprostinil, recommended dosage amounts for subjects suffering from pulmonary hypertension and instructions on coordination of individual's breathing and actuation of the metered dose inhaler.

The present invention can be illustrated in more detail by the following example, however, it should be understood that the present invention is not limited thereto.

Example 1

Open Label Study Upon Acute Safety, Tolerability and Hemodynamic Effects of Inhaled Treprostinil Delivered in Seconds

A study was conducted of acute vasodilator challenge during right heart catheter investigation to determine the safety, tolerability and pulmonary vasodilatory potency of inhaled treprostinil applied in seconds by a soft mist inhaler (SMI-TRE). The study produced evidence for a long lasting

favourable effect of SMI-TRE on pulmonary hemodynamics in absence of systemic side effects and gas exchange disruptions.

Summary:

Inhaled nitric oxide (20 ppm; n=45) and inhaled treprostinil sodium (TRE; n=41) or placebo (n=4) were applied once during right heart catheter investigation. TRE was delivered in 2 breaths (1000 μg/ml aerosol concentration; 30 μg dose; n=12), 3 breaths (1000 μg/ml; 45 μg; n=9) or 2 breaths (2000 μg/ml; 60 μg; n=20) from a Respimat® SMI. Pulmonary hemodynamics and blood gases were measured at defined time points, observation time following TRE application was 120 minutes. TRE doses of 30 μg, 45 μg and 60 μg reduced pulmonary vascular resistance (PVR) to 84.4±8.7%, 71.4±17.5% and 77.5±7.2% of baseline values, respectively (mean±95% confidence interval). The 120 minute area under the curve for PVR for placebo, 30 μg, 45 μg and 60 μg TRE was 1230±1310, −870±940, −2450±2070 and −2000±900 min %, respectively. Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes. Reduction of systemic vascular resistance and pressure was negligible, showing a high pulmonary selectivity for SMI-TRE. Intrapulmonary selectivity was also provided by SMI-TRE as ventilation/perfusion matching, assessed by the multiple inert gas elimination technique in 5 patients with gas exchange problems, was not significantly different after SMI-TRE compared to inhaled nitric oxide or no treatment. No significant side effects were observed.

Conclusions: The acute application of inhaled treprostinil with a metered dose inhaler in 2-3 breaths was safe, well tolerated and induced a strong and sustained pulmonary selective vasodilation.

Methods and Patients

A total number of 45 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics were: female to male ratio (f/m)=29/16, age 59±2.3 years, pulmonary artery pressure (PAP) 45±1.8 mmHg, pulmonary vascular resistance (PVR) 743±52 dynes·s·cm^{-5}, pulmonary artery wedge pressure (PAWP) 8.6±0.5 mmHg, central venous pressure (CVP) 6.4±0.7 mmHg, cardiac output (CO) 4.5±0.2 l/min, central venous oxygen saturation (SvO2) 62.3±1.2 mmHg (mean±Standard Error of the Mean). Disease etiologies were idiopathic PAH (iPAH) (n=13), PAH other (n=11), chronic thromboembolic pulmonary hypertension (CTEPH) (n=17) and pulmonary fibrosis (n=4). Table 1 presents the patient characteristics of the different groups.

TABLE 1

Patient characteristics of the different treatment groups. Data are given as mean ± Standard Error of the Mean (SEM).

	Placebo (n = 4)	30 μg TRE (n = 12)	45 μg TRE (n = 9)	60 μg TRE (n = 20)
Age [years]	61 ± 8	53.9 ± 3.9	54.2 ± 5.7	65.5 ± 3.1
PAP [mmHg]	49.5 ± 10.1	45 ± 3.1	54.3 ± 2.8	39.7 ± 2.0
PVR [Dynes]	896 ± 163	597 ± 53.9	1049 ± 107	663 ± 81
CO [l/min]	4.46 ± 0.9	5.2 ± 0.4	3.9 ± 0.4	4.4 ± 0.3
SAP [mmHg]	98 ± 8.1	90.1 ± 3.2	82.8 ± 3.9	86.1 ± 2.0
SaO2 [%]	85.3 ± 4.5	90.0 ± 1.1	89.6 ± 1.1	90.6 ± 0.5
SvO2 [%]	57.5 ± 3.9	66.0 ± 1.6	59.1 ± 3.4	62.5 ± 1.6

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation.

Baseline values were determined 20-30 minutes after placement of the catheter. Heart rate, pulmonary and systemic blood pressure and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Pharmacological interventions included the inhalation of 20 ppm nitric oxide (NO) after evaluation of baseline parameters (n=45) and the consecutive inhalation of placebo (n=4), 30 μg SMI-TRE (n=12), 45 μg SMI-TRE (n=9) or 60 μg (n=20) SMI-TRE. Placebo and treprostinil was applied with the Respimat® SMI. For filling of this device with treprostinil sodium, the placebo solution was withdrawn from the device with a syringe and treprostinil solution was injected into the device under sterile conditions. Aerosol quality was controlled before and after refilling of the SMI devices by laser diffractometry, see e.g. Gessler T., Schmehl T., Hoeper M. M., Rose F., Ghofrani H. A., Olschewski H. et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur. Respir. J. 2001; 17:14-19 incorporated herein in its entirety. The aerosol sizes before (placebo) and after filling (treprostinil) were unchanged. The aerosol particles mass median aerodynamic diameter of treprostinil-aerosol was 4-5 μm, which can be at the upper limit for alveolar deposition. The aerosol volume delivered by one cycle from the SMI was 15 μl. The solution used for aerosol generation was prepared from treprostinil sodium salt using a standard protocol. The SMI was either filled with a concentration of 1000 μg/ml treprostinil sodium (one aerosol puff=15 μg TRE) or with 2000 μg/ml (one puff=30 μg TRE). The different doses were applied as 2 puffs 1000 μg/ml (30 μg), 3 puffs 1000 μg/ml (45 μg) and 2 puffs 2000 μg/ml (60 μg). The placebo was inhaled as 2 puffs from a placebo-SMI. Hemodynamics and gas-exchange parameters were recorded for 120 minutes after TRE inhalation. This study used the Respimat® device, because the implemented "soft mist" technology was well suited for the deposition of such highly active drugs like prostanoids.

The impact of SMI-TRE on ventilation-perfusion matching was assessed in five patients (30 μg TRE, n=2; 45 μg TRE, n=1; 60 μg TRE, n=2) with pre-existing gas exchange problems by use of the multiple inert gas elimination technique (MIGET), see e.g. Wagner P D, Saltzman H A, West J B. Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol. 1974; 36:588-99; Ghofrani H A, Wiedemann R, Rose F, Schermuly R T, Olschewski H, Weissmann N et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002; 360:895-900, both incorporated herein in their entirety.

Statistics:

Mean values, standard deviation, standard error of the mean and 95% confidence intervals were calculated. Statistical analysis was done by use of a paired t-test.

Results:

The inhalation of treprostinil sodium from the metered dose inhaler (SMI-TRE) was well tolerated, only mild and transient cough for a maximum of one minute was reported. No systemic side effects like headache, flush, nausea or dizziness were observed.

Two to three breaths of SMI-TRE induced a strong pulmonary vasodilation that outlasted the observation time of 120 minutes (45 and 60 μg). The lower dose of 30 μg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal pulmonary vasodilation was comparable. In contrast, placebo inhalation did not induce pulmonary vasodilation. In fact a slight increase in PVR over the time of the right heart catheter investigation could be recorded following placebo inhalation (FIG. **1**). The effect of SMI-TRE on systemic vascular resistance and

pressure was very small and not clinically significant. Cardiac output was significantly increased over the whole observation period, whereas heart rate was rather unchanged. Gas exchange was not influenced by SMI-TRE (FIG. **2**). The maximal changes in hemodynamic and gas-exchange parameters compared to baseline values are depicted in Table 2.

TABLE 2

Extremes of the relative changes of hemodynamic and gas exchange parameters compared to baseline after inhalation of Placebo (n = 4), 30 μg treprostinil (n = 12), 45 μg treprostinil (n = 9) and 60 μg treprostinil (n = 20). Highest (max) and lowest (min) values during the observation period are shown. Data are given as percent of baseline values (mean ± SEM).

	Placebo	30 μg TRE	45 μg TRE	60 μg TRE
PAP (min)	99.4 ± 3.0	83.4 ± 3.2	77.6 ± 6.8	79.5 ± 2.4
PVR (min)	101.4 ± 1.9	84.4 ± 4.4	71.4 ± 8.9	77.5 ± 3.7
CO (max)	99.7 ± 1.1	108.8 ± 3.8	108.6 ± 5.6	103.8 ± 2.0
SVR (min)	104.3 ± 4.3	97.7 ± 4.2	92 ± 3.9	91.3 ± 2.1
SAP (min)	102.7 ± 1.7	97.3 ± 1.9	96.1 ± 1.5	93.6 ± 2.9
HR (max)	105 ± 2.1	106.1 ± 2.9	99.1 ± 2.4	101.1 ± 0.9
SaO2 (min)	98.2 ± 0.4	101 ± 0.3	94.4 ± 1.8	95.8 ± 0.9
SvO2 (max)	104.5 ± 1.4	102.4 ± 1.3	104.5 ± 4.4	102 ± 1.0

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation.

The areas under the curve for PVR were calculated for placebo and the different SMI-TRE doses over the 120 minute observation period (FIG. 3). A dose effect of SMI-TRE with a trend to a more sustained effect with the two highest doses could be observed.

The inhalation of a highly concentrated aerosol can be in theory prone to disturbances of gas exchange because the deposition of even small amounts of aerosol may deliver high doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This would then lead to increased shunt flow or increase of low ventilation/perfusion (V/Q) areas. This question was addressed in five patients with the multiple inert gas elimination technique (MIGET), the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected for pre-existing gas exchange limitations. Characteristics of these patients were: PAP 54.6±3.2 mmHg, PVR 892±88 dynes, SaO2 91.7±0.5%, SvO2 65.2±1.8%. Etiologies were iPAH (n=1), CTEPH (n=3), pulmonary fibrosis (n=1). The maximal relative reduction of SaO2 after inhalation of SMI-TRE in these patients was −3.8±1.5% compared to baseline values. Shunt flow at baseline, NO-inhalation and 60 minutes after SMI-TRE was 6.4±4.3%, 5.4±3.0% and 8.3±3.4%, respectively (mean±95% confidence interval; FIG. **4**).

No significant increase in low V/Q areas or shunt fraction after inhalation of SMI-TRE was observed, in fact the distribution of perfusion was not different to that at baseline and during nitric oxide inhalation. This proves an excellent intrapulmonary selectivity of SMI-TRE, which is also reflected by unchanged arterial oxygen saturation.

Conclusion:

Treprostinil is tolerated at high doses with no systemic side effects. The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution. Treprostinil can be applied by a metered dose inhaler, such as Respimat® soft mist inhaler.

Example 2

Investigation of the Effects of Inhaled Treprostinil on Pulmonary Hemodynamics and Gas Exchange in Severe Pulmonary Hypertension

This study investigated the effects of inhaled treprostinil on pulmonary vascular resistance in severe pulmonary hypertension and addressed systemic effects and gas exchange as well as tolerability and efficacy of high doses of treprostinil given in short time. A total of 123 patients with a mean pulmonary artery pressure of about 50 mmHg were investigated in three separate randomized studies. Inhaled treprostinil exerted potent sustained pulmonary vasodilation with excellent tolerability and could be safely applied in a few breaths or even one breath.

Summary:

Three different studies were conducted on a total of 123 patients by means of right heart catheterization: i) a randomized crossover-design study (44 patients), ii) a dose escalation study (31 patients) and iii) a study of reduction of inhalation time while keeping the dose fixed (48 patients). The primary endpoint was the change in pulmonary vascular resistance (PVR).

The mean pulmonary artery pressure of the enrolled patients was about 50 mmHg. Hemodynamics and patient characteristics were similar in all studies. In study i) TRE and Iloprost (ILO), at an inhaled dose of 7.5 μg, displayed comparable PVR decrease, with a significantly different time course (p<0.001), TRE exhibiting a more sustained effect on PVR (p<0.0001) and less systemic side effects. In study ii) placebo, 30 μg, 60 μg, 90 μg or 120 μg TRE were applied with drug effects being observed for 3 hours after inhalation. A near-maximal acute PVR decrease was observed at 30 μg TRE. In study iii) TRE was inhaled with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. 15 μg TRE was inhaled with 18 pulses (TRE concentration 100 μg/ml), 9 pulses (200 μg/ml), 3 pulses (600 μg/ml), 2 pulses (1000 μg/ml) or 1 pulse (2000 μg/ml), each mode achieving comparable, sustained pulmonary vasodilation.

Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at doses, which may be inhaled in a few or even one breath. Inhaled treprostinil is advantageous to inhaled iloprost in terms of duration of effect and systemic side effects. Inhaled treprostinil is well tolerated in concentrations up to 2000 mg/ml (bringing down inhalation time to a single breath) and in high doses (up to 90 μg).

Methods:

All inhalations were performed with the OPTINEB® ultrasonic nebulizer (Nebutec, Elsenfeld, Germany).

Study i) was a randomized, open-label, single-blind crossover study. The primary objective was to compare the acute hemodynamic effects and the systemic side effects of inhaled treprostinil with inhaled iloprost at comparable doses. A total number of 44 patients with moderate to severe precapillary pulmonary hypertension were enrolled. Patient characteristics and hemodynamic as well as gas exchange parameters are outlined in Table 3.

TABLE 3

Patient characteristics, hemodynamic parameters and gas exchange values at baseline, before challenge with inhalative prostanoids.

	N	Age	Gender f/m	Etiology i/o/t/f	PAP [mmHg]	PVR [dyn * s * cm^{-5}]	SAP [mmHg]	CVP [mmHg]	PAWP [mmHg]	CO [l/min]	SaO2 [%]	SvO2 [%]
1a	14	55.1 ± 4.8	11/3	4/4/2/4	53.8 ± 3.1	911 ± 102	95.4 ± 3.6	7.4 ± 1	8.0 ± 0.8	4.3 ± 0.4	93.8 ± 2	63.9 ± 2.4
1b	14	54.1 ± 3.3	10/4	1/6/5/2	47.4 ± 3.8	716 ± 80	90.6 ± 3.3	5.9 ± 1.4	6.4 ± 0.7	4.7 ± 0.4	92 ± 1	64.4 ± 2.3
1c	16	56 ± 2.9	7/9	6/3/6/1	47.5 ± 4.5	777 ± 102	92 ± 4.5	8.3 ± 1.4	8.6 ± 1.4	4.4 ± 0.5	91.4 ± 0.9	59.8 ± 2.6
2a	8	60.8 ± 4	4/4	2/2/3/1	51.9 ± 4.9	849 ± 152	95.9 ± 4.8	7.6 ± 1.4	11.1 ± 1.7	4.4 ± 0.6	89.6 ± 2.8	60.1 ± 2.8
2b	8	52.8 ± 6.6	6/2	1/3/3/1	49 ± 4	902 ± 189	92.4 ± 2.4	4.8 ± 1.1	7.2 ± 1.3	4.0 ± 0.4	92.4 ± 2.4	62.5 ± 1.7
2c	6	56.8 ± 5.9	4/2	0/2/2/2	44.2 ± 3.5	856 ± 123	96.3 ± 3.9	5 ± 1.1	6 ± 1	3.8 ± 0.3	92.8 ± 1.5	63.6 ± 1.8
2d	6	51.2 ± 3.8	4/2	2/2/2/0	55.5 ± 4.9	940 ± 110	91.2 ± 8.1	11.2 ± 1.2	10 ± 0.7	3.9 ± 0.4	92 ± 1.9	62 ± 5.8
2e	3	57.3 ± 9.1	1/2	0/1/0/2	45.3 ± 5.2	769 ± 267	99 ± 3.2	5 ± 2.1	9 ± 0.6	4.5 ± 0.6	94.2 ± 1.3	66.3 ± 1.5
3a	6	52.7 ± 6.6	4/2	2/4/0/0	53.8 ± 6.7	928 ± 145	92.7 ± 7.9	8.7 ± 2.7	8.8 ± 1.3	4.2 ± 0.6	90.4 ± 2.8	64.8 ± 4.3
3b	6	58.3 ± 3.5	4/2	3/1/1/1	54.2 ± 6.1	808 ± 156	94.3 ± 2.8	7 ± 1.4	10 ± 1.3	5 ± 0.7	91.9 ± 0.7	63.5 ± 2.9
3c	21	57.4 ± 5.6	8/3	7/7/6/1	46.1 ± 2.5	900 ± 99	88 ± 2.8	9 ± 1.4	9.2 ± 0.5	3.7 ± 0.3	91.7 ± 0.5	59.7 ± 2
3d	7	55.6 ± 5.8	3/4	0/4/3/0	53.1 ± 7.1	732 ± 123	91.4 ± 5.6	7.9 ± 3.1	8.6 ± 1.3	5 ± 0.4	90.7 ± 1.4	61.3 ± 3.7
3e	8	59 ± 5.2	7/1	0/4/4/0	45.1 ± 3.9	733 ± 114	92.8 ± 6.8	4.6 ± 0.8	8.1 ± 1.1	4.3 ± 0.2	90.7 ± 0.8	66.3 ± 2.8

Group 1 corresponds to study i); randomized crossover study comparing inhaled iloprost (ILO) and inhaled treprostinil (TRE).
a = 7.5 g ILO vs. 7.5 μg TRE,
b = 7.5 g ILO vs. 15 μg TRE (6 min inhalation time),
c = 7.5 g ILO vs. 15 μg TRE (3 min inhalation time).
Group 2 corresponds to study ii); evaluation of maximal tolerated dose of TRE.
a = placebo inhalation,
b = 30 μg TRE,
c = 60 μg TRE,
d = 90 μg TRE,
e = 120 μg TRE.
Group 3 corresponds to study iii); reduction of inhalation time by increase of TRE concentration, aiming at a total inhaled dose of 15 μg.
a = 18 pulses of 100 μg/ml TRE,
b = 9 pulses of 200 μg/ml TRE,
c = 3 pulses of 600 μg/ml TRE,
d = 2 pulses of 1000 μg/ml TRE,
e = 1 pulse 2000 μg/ml TRE.
Etiology of pulmonary hypertension was classified as idiopathic PAH (i), PAH of other causes (o), chronic thromboembolic PH (t), and pulmonary fibrosis (f).

Each patient inhaled both iloprost and treprostinil on the same day during right heart catheter investigation; the drugs were administered consecutively with a one hour interval between the drug applications. One half of the study patients initially inhaled treprostinil and then inhaled iloprost (n=22), while the other half initially inhaled iloprost and then inhaled treprostinil (n=22). Patients were randomized to one of the two groups and blinded as to the study drugs. Drug effects were monitored for 60 minutes after each inhalation. Iloprost was inhaled at 4 μg/ml (6 min inhalation time; n=44) and treprostinil was inhaled at a concentration of 4 μg/ml (6 min inhalation; n=14), 8 μg/ml (6 min inhalation; n=14) or 16 μg/ml (3 min inhalation; n=16). Based on previous biophysical characterization of the ultrasonic device with iloprost- and treprostinil-solution, this corresponds to a total inhaled dose of 7.5 μg iloprost and treprostinil (4 μg/ml) and 15 μg treprostinil (8 μg/ml and 16 μg/ml), respectively.

Study ii) was a randomized, open-label, single blind, placebo controlled study. The primary objectives were to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well tolerated dose (30 μg) and to explore the highest tolerated single dose. A total number of 31 patients inhaled either placebo or treprostinil; each patient received one inhalation. The first 16 patients were randomized to 30 μg TRE (16 μg/ml, n=8) or placebo (stock solution in a concentration corresponding to TRE 16 μg/ml). Subsequent patients received 60 μg TRE (32 μg/ml; n=6), 90 μg TRE (48 μg/ml; n=6) and 120 μg TRE (64 μg/ml; n=3). Inhalation time was 6 minutes in all groups. Hemodynamics and gas-exchange as well as arterial treprostinil concentrations were recorded for 180 minutes.

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15 μg dose of inhaled treprostinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (OPTINEB®, Nebutec, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15 μg was either generated during 18 cycles (OPTINEB® filled with 100 μg/ml TRE, n=6), 9 cycles (200 μg/ml TRE, n=6), 3 cycles (600 μg/ml TRE, n=21), 2 cycles (1000 μg/ml TRE, n=7) or 1 cycle (2000 μg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120-180 minutes.

Treprostinil plasma concentrations were assessed in study ii) at 10, 15, 30, 60 and 120 minutes after inhalation. Treprostinil quantification was done by Alta Analytical Laboratory (El Dorado Hills, Calif., USA) with a validated liquid chromatography atmospheric-pressure ionization tandem mass spectrometry as previously described Wade M., et al. J. Clin. Pharmacol. 2004; 44:503-9. Mixed venous blood was drawn at the depicted time points (FIG. **11**) after inhalation, centrifuged and the plasma frozen at −80° C. until temperature controlled shipping on dry ice.

Statistics:

For statistical analysis of study i) the repeated PVR measurements after inhaled iloprost and treprostinil were subjected to a three-factorial analysis of variance (ANOVA; factors: time (A), drug (B), treprostinil concentration (C)) to avoid multiple testing. The time to maximum PVR decrease after inhalation of iloprost versus treprostinil was compared by paired t-test. Area under the curve (AUC) was calculated from start of inhalation until 60 min after inhalation. Means, standard error of the mean (SEM) and 95% confidence

intervals were calculated. For study ii) and iii) areas between curves (ABC) were calculated between placebo inhalation (study ii) and the respective treprostinil inhalation until 180 min (study ii)) and 120 min (study iii)) after end of inhalation.

Results:

The inhalation of iloprost as well as treprostinil in study i) resulted in a rapid decrease in PVR and PAP (FIG. **5**-**7**). No significant differences were observed for the areas under the curve (AUC) of PVR decrease after inhalation of 7.5 μg TRE in 6 minutes (AUC −12.6±7.0%), 15 μg TRE in 6 minutes (AUC −13.3±3.2%) and 15 μg TRE in 3 minutes (AUC −13.6±4.3%). The AUC for PVR after the inhalation of 7.5 μg iloprost in 6 minutes was −7.7±3.7% (mean±95% confidence interval). An overview of the pooled data of treprostinil inhalation as compared to iloprost inhalation is given in FIG. **7**. The maximum effect of iloprost and treprostinil on PVR was comparable but this effect was reached significantly later after treprostinil inhalation (18±2 min) compared to iloprost (8±1 min; mean±SEM, p<0.0001) and lasted considerably longer (after 60 min, PVR values in the treprostinil group had not yet returned to baseline). The increase in cardiac output was less acute but prolonged after treprostinil inhalation. Systemic arterial pressure (SAP) was unaffected by treprostinil inhalation, whereas a transient decrease was observed after iloprost inhalation. Iloprost and treprostinil did not affect gas exchange. Three-factorial ANOVA for PVR demonstrated a significant difference between repeated measurements after inhalation ($p_{(A)}<0.0001$), no significant difference between drugs ($p_B=0.1$), no difference between treprostinil concentrations ($p_{(C)}=0.74$) and a significant drug×time interaction ($p_{(A\times B)}<0.0001$). This translates into a significant effect of both drugs on PVR with comparable drug potency but a prolonged drug effect of treprostinil compared to iloprost.

In this study the occasionally observed mild side effects of iloprost inhalation at the given dose (transient flush, headache) were not observed with inhaled treprostinil. Bad taste was reported by most of the patients after inhalation of TRE. This was later found to be attributable to the metacresol preservative contained in the treprostinil solution.

In study ii) pharmacodynamics of inhaled placebo or treprostinil were observed for 180 minutes. Placebo inhalation was followed by a gradual increase in PVR over the entire observation time. Due to reduced patient numbers in the 120 μg TRE group (because of side effects, see below), the hemodynamic values for this group were not included in the graphs of this study (FIG. **8**-**9**). All TRE doses lead to comparable maximal decreases of PVR to 76.5±4.7% (30 μg), 73.7±5.8% (60 μg), 73.3±4.3% (90 μg) and 65.4±4.1% (120 μg) of baseline values. An extended duration of pulmonary vasodilation was noted, surpassing the 3 hour observation period for the 60 μg and 90 μg (and 120 μg) TRE doses, whereas in the 30 μg dose group the hemodynamic changes had just returned to baseline within this period. Even at the highest doses, TRE had only minor effects on systemic arterial pressure (FIG. **8**). Cardiac output was increased to a maximum of 106.8±3.2% (30 μg), 122.9±4.3% (60 μg), 114.3±4.8% (90 μg) and 111.3±3.9% (120 μg TRE). The areas between the response curves after placebo versus TRE inhalation were calculated for PVR, PAP, SVR and SAP (FIG. **9**). Areas between the curves for PVR were not significantly different for 30 μg, 60 μg and 90 μg TRE, a nearly maximal effect on PVR was already observed with 30 μg TRE. Effects on PAP and SAP were small and did not show a dose-response relationship. Gas exchange was not affected at doses up to 90 μg TRE, but arterial oxygen saturation was significantly decreased at a dose of 120 μg TRE in all 3 patients. Further dose increments were omitted due to this side effect and severe headache in one patient.

Again, bad taste of the TRE aerosol was reported by most patients. Other side effects were flushing (n=1; 30 μg TRE), mild transient cough (n=3; 60 μg TRE), mild transient bronchoconstriction that resolved after one inhalation of fenoterol (n=1; 30 μg TRE), moderate bronchoconstriction that resolved after one inhalation of fenoterol (n=1; 120 μg TRE), and severe headache (n=1; 120 μg TRE). The bad taste, the bronchoconstriction and the drop in SaO2 was attributed to metacresol in the original TRE solution. With the use of a metacresol-free solution of TRE (University Hospital Giessen, Germany; produced according to the manufacturer's protocol) in the following study, these side effects did no longer occur.

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified OPTINEB® inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000 μg/ml without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough (n=6), mild headache (n=2) and mild jaw pain (n=1).

The reduction of PVR and PAP was comparable between all groups (FIG. **10**). TRE inhalation reduced PVR to 76.3±5.6% (18 pulses, 100 μg/ml), 72.9±4.9% (9 pulses, 200 μg/ml), 71.2±6.0% (3 pulses, 600 μg/ml), 77.4±4.5% (2 pulses, 1000 μg/ml) and 80.3±5.2% (1 pulse, 2000 μg/ml). PAP was reduced to 84.2±4.5% (18 pulses, 100 μg/ml), 84.2±4.1% (9 pulses, 200 μg/ml), 81.1±4.1% (3 pulses, 600 μg/ml), 86±4% (2 pulses, 1000 μg/ml) and 88±5.4% (1 pulse, 2000 μg/ml). Cardiac output was moderately increased in all groups, whereas systemic arterial pressure was not significantly affected.

The areas between the curves (ABC) for changes in hemodynamic and gas-exchange parameters after inhalation of 15 μg TRE versus placebo were calculated for an observation time of 120 minutes (FIG. **11**). The ABC for both PVR and PAP was comparable between all groups.

Pharmakokinetic results from study ii): Peak plasma concentrations of treprostinil were found 10-15 minutes after inhalation. Maximal treprostinil plasma concentrations (C_{max}) for the 30 μg, 60 μg, 90 μg and 120 μg doses were 0.65±0.28 ng/ml (n=4), 1.59±0.17 ng/ml (n=4), 1.74 ng/ml (n=1) and 3.51±1.04 ng/ml (n=2), respectively (mean±SEM; FIG. **12**).

Discussion:

These studies investigated whether i) the acute effects of inhaled treprostinil would be comparable to or possibly advantageous over inhaled iloprost in pulmonary hypertensive patients, ii) the inhaled prostanoid dose might be increased without substantial local or systemic side effects, and iii) if the time of inhalation, which is 6-12 minutes for iloprost, could be reduced significantly by increasing the concentration of treprostinil aerosol.

The patient population in these studies included different forms of precapillary pulmonary hypertension. All these patients had a need for therapy of pulmonary hypertension and reflected the typical population of a pulmonary hyper-

tension center. No major differences in patient characteristics or hemodynamic baseline values existed between the different groups (table 3).

In study i) it was shown that the inhalation of treprostinil and iloprost in similar doses resulted in a comparable maximum pulmonary vasodilatory effect. However, marked differences in the response profile were noted. The onset of the pulmonary vasodilatory effect of inhaled treprostinil was delayed compared to iloprost, but lasted considerably longer, with the PVR decrease continuing beyond the one-hour observation period. Although the average dose of treprostinil was higher than the iloprost dose, no systemic effects were noted after treprostinil inhalation, whereas flush and transient SAP decrease, accompanied by more prominent cardiac output increase, occurred after iloprost inhalation. Such side effects were more prominent than in previous studies with inhaled iloprost. This may have been caused by the fact that the iloprost dose used in this study was 50% higher than the recommended single inhalation dose (5 μg) and that the preceding treprostinil inhalation may have added to the systemic side effects caused by the iloprost inhalation. Surprisingly, with TRE there was no such systemic side effect, although the average effect on PVR was as potent as with iloprost.

This study used a cross-over design in order to minimize the effects of inter-individual differences in response to prostanoids. The short observation period of 1 hour was used to avoid an uncomfortably long catheter investigation. As a study limitation, the short observation interval may have caused carryover effects of the first to the second period as suggested by FIG. **5**. However, this still allowed for the interpretation of the study, that both drugs are potent pulmonary vasodilators and that treprostinil effects are significantly sustained compared to the iloprost effects.

The longer duration of action and the virtual absence of side effects (except the bitter taste of treprostinil aerosol, later attributed to metacresol) encouraged increasing the applied treprostinil dose in study ii). Observation time was extended to 3 hours to obtain precise pharmacodynamic data. Inhaled treprostinil resulted in a strong pulmonary vasodilation that outlasted the observation time of 3 hours when compared to placebo inhalation. Surprisingly, inhaled treprostinil was tolerated in doses up to 90 μg.

Study iii) successfully demonstrated that the inhalation time could be reduced to literally one single breath of 2000 μg/ml treprostinil solution, thereby applying a dose of 15 μg. This drug administration with a single breath induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation. Side effects were minor, of low frequency and not related to drug concentration. It was a surprising finding that such high concentrations of treprostinil were so well tolerated.

Conclusion:

Inhaled treprostinil can be applied in high doses (up to 90 μg) with a minimal inhalation time. Inhaled treprostinil exerts high pulmonary selectivity and leads to a long-lasting pulmonary vasodilation.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

2. The method of claim **1**, wherein the inhalation device is a soft mist inhaler.

3. The method of claim **1**, wherein the inhalation device is a pulsed ultrasonic nebulizer.

4. The method of claim **1**, wherein the inhalation device is a dry powder inhaler.

5. The method of claim **1**, wherein the inhalation device is a pressurized metered dose inhaler.

6. The method of claim **4**, wherein the formulation is a powder.

7. The method of claim **6**, wherein the powder comprises particles less than 5 micrometers in diameter.

8. The method of claim **1**, wherein the formulation contains no metacresol.

* * * * *

EXHIBIT 8

Deposition of:

Lewis J. Rubin, M.D.

September 15, 2021

In the Matter of:

United Therapeutics Corporation vs Liquidia Technologies Inc

Veritext Legal Solutions
800-734-5292 | calendar-dmv@veritext.com |

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS :
CORPORATION, : C.A. No. 20-755-RGA
Plaintiff, :
:
vs. :
LIQUIDIA :
TECHNOLOGIES, INC., :
Defendant. :

VIDEOTAPE DEPOSITION OF:
LEWIS J. RUBIN, M.D.
NEW YORK, NEW YORK
WEDNESDAY, SEPTEMBER 15, 2021

REPORTED BY:
SILVIA P. WAGE, CCR, CRR, RPR
JOB NO. 4792048

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

SEPTEMBER 15, 2021
9:10 a.m.

Videotape deposition of LEWIS J. RUBIN, M.D., held at the offices of COOLEY LLP, 55 Hudson Yards, 44th Floor Conference Room, New York, New York, pursuant to agreement before SILVIA P. WAGE, a Certified Shorthand Reporter, Certified Realtime Reporter, Registered Professional Reporter, and Notary Public for the States of New Jersey, New York and Pennsylvania.

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

A P P E A R A N C E S:

GOODWIN PROCTER LLP
Attorneys for Plaintiff
1900 N Street N.W.
Washington D.C. 20036
(202) 346-4216
Wjackson@goodwinlaw.com
Hgunn@goodwinlaw.com
BY: WILLIAM JACKSON, ESQ.
BY: HARRISON GUNN, ESQ.

COOLEY LLP
Attorneys for Defendant
1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004
(202) 776-2982
Ssukduang@cooley.com
Bcazakoff@cooley.com
BY: SANYA SUKDUANG, ESQ.
BY: BRITTANY CAZAKOFF, ESQ.

OSTRAGER CHONG FLAHERTY & BROITMAN P.C.
Attorneys for Deponent
437 Madison Avenue
New York, New York
(212) 681-0600
Gostrager@ocfblaw.com
BY: GLENN OSTRAGER, ESQ.

A L S O P R E S E N T
CARLOS KING
VIDEOGRAPHER

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

THE VIDEOGRAPHER: Good morning. We are going on the record at 9:10 a.m. on September 15, 2021. 09:08:17 09:08:18 09:08:23

Please note that the microphones are sensitive and may pick up whispering, private conversations and cellular interference. Please turn off all cell phones or place them away from the microphones, as they can interfere with the deposition audio. 09:08:26 09:08:27 09:08:30 09:08:33 09:08:36 09:08:38

Audio and video recording will continue to take place unless all parties agree to go off the record. 09:08:39 09:08:40 09:08:42

This is Media Unit No. 1 of the video recorded deposition of Mr. Lewis J. Rubin taken by Counsel for Defendant in the matter of United Therapeutics Corporation versus Liquidia Technologies Inc., filed in the United States District Court for the District of Delaware, Case No. 20-755-RGA. 09:08:44 09:08:47 09:08:51 09:08:56 09:08:59 09:09:01 09:09:09

This deposition is being held at the offices of Cooley LLP located at 55 Hudson Yards, New York, New York. 09:09:12 09:09:14 09:09:18

My name is Carlos King from the firm of Veritext and I'm the Videographer. The Court 09:09:20 09:09:21

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

Reporter is Silvia Wage also from Veritext. I'm not authorized to administer an oath. I'm not related to any party in this action. Nor am I financially interested in the outcome. 09:09:24 09:09:26 09:09:29 09:09:31

Counsel and all present in the room and everyone attending remotely will now state their appearance and affiliation for the record. If there are any objections to the proceedings, please state them at the time of your appearance beginning with the noticing attorney. 09:09:32 09:09:35 09:09:37 09:09:39 09:09:42 09:09:43

MR. SUKDUANG: Sanya Sukduang and Brittany Cazakoff from Cooley LLP on behalf of Defendant Liquidia. 09:09:46 09:09:48 09:09:51

MR. OSTRAGER: Glenn Ostrager of the firm of Ostrager Chong Flaherty & Broitman on behalf of Dr. Rubin. 09:09:55 09:09:56 09:09:57

MR. JACKSON: William Jackson and Harrison Gunn from the law firm of Goodwin Procter LLP on behalf of United Therapeutics. 09:10:00 09:10:01 09:10:04

THE VIDEOGRAPHER: Can the Court Reporter please swear in the witness. 09:10:08 09:10:09

LEWIS J. RUBIN, M.D., 09:10:09

690 Orchard Shore Road, Colchester, Vermont 05446, after having been duly sworn, was 09:10:09 09:10:09

HIGHLY CONFIDENTIAL - LEWIS J. RUBIN, M.D.

examined and testified as follows: 09:10:16

THE STENOGRAPHER: Thank you. 09:10:16

You may proceed. 09:10:18

EXAMINATION BY MR. SUKDUANG: 09:10:19

Q. Good morning, Dr. Rubin. 09:10:19

A. Good morning. 09:10:19

Q. My name is Sanya Sukduang. And I'm 09:10:20 here to ask you some questions today regarding 09:10:23 some of the work you've done on pulmonary 09:10:26 arterial hypertension and treprostinil, okay? 09:10:30

A. Sure. 09:10:33

Q. I understand you've been deposed in 09:10:34 the past; is that correct? 09:10:36

A. Yes. 09:10:38

Q. Okay. It's probably been a while, so 09:10:38 I'm going to go a little bit of the ground rules 09:10:40 just to refresh everyone's memory. 09:10:44

So, as I said before, I'm here to ask 09:10:45 you questions and I ask that you answer them to 09:10:47 the best of your ability; is that okay? 09:10:50

A. Sure. 09:10:52

Q. If I ask you something and my 09:10:53 question is unclear or you don't understand what 09:10:54 I'm -- what I'm asking, please let me know and 09:10:58

A. Yes. 10:01:22

Q. Okay. Under the umbrella of PH, pulmonary hypertension, other than PVH and PAH, are there any other manifestations that would fall under that umbrella? 10:01:22 10:01:25 10:01:27 10:01:29

A. Well, I wouldn't say, "manifestations." I would say etiologies or conditions, again, according to the classification. 10:01:31 10:01:34 10:01:41 10:01:45

So classification very simply is -- No. 1 is pulmonary arterial hypertension, PAH, and then the subclassification lists a number of different disease processes that cause PAH. 10:01:46 10:01:51 10:01:54 10:01:57

No. 2 is pulmonary hypertension due to left heart disease and that, in general, causes pulmonary venous hypertension, but it's not the only cause of pulmonary venous hypertension. It's the most common but it's not the only one. 10:02:03 10:02:07 10:02:13 10:02:20 10:02:23 10:02:26

And then Group 3 is chronic lung diseases that can cause pulmonary hypertension, emphysema, pulmonary fibrosis, those sorts of things, cystic fibrosis. 10:02:26 10:02:29 10:02:32 10:02:38

Group 4 is chronic thromboembolic 10:02:41

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pulmonary hypertension. So blood clots that are chronic that plug up the vasculature in the lungs and cause the back pressure to be elevated. That's intrinsic clots within the lungs. 10:02:44 10:02:48 10:02:53 10:03:00

And Group 5 is a grab bag of miscellaneous causes, less common diseases that can be associated with pulmonary hypertension. Cycle cell disease is one, sarcoidosis is another. There is a list of, you know, relatively uncommon diseases that, you know, the experts will see from time to time, but, you know, that practitioners in the field it's worth their, at least, having some awareness that can be associated. 10:03:04 10:03:06 10:03:14 10:03:15 10:03:20 10:03:24 10:03:27 10:03:32 10:03:37 10:03:40

Q. I want to turn to your discussion about or your testimony regarding working on FDA approved drugs for PAH. 10:03:46 10:03:47 10:03:53

A. Uh-huh. 10:03:55

Q. Okay. In your testimony, you mentioned you worked on the first drug FDA approved for PAH. 10:03:57 10:04:01 10:04:04

Do you recall that? 10:04:06

A. Yes. 10:04:07

Q. What was that drug? 10:04:07

EXHIBIT 9

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,)
Plaintiff,)C.A. No. 23-975(RGA)
v.)
LIQUIDIA TECHNOLOGIES, INC.,)

Washington, D.C.

Sunday, March 10, 2024

Deposition of STEVEN D. NATHAN, M.D., a witness herein, called for examination by counsel for the Defendant in the above-entitled matter, pursuant to notice, the witness being duly sworn by Barbara J. Moore, a Notary Public in and for the District of Columbia, taken at the offices of GOODWIN PROCTOR, LLP, 1900 N Street, NW, Washington, D.C., at 9:00 a.m., and the proceedings being taken down by Stenotype by BARBARA MOORE, CRR, RMR, and transcribed under her direction.

APPEARANCES:

On Behalf of the Plaintiff:
McDermott Will & Emery
BY: ARTHUR P. DYKHUIS, ESQ.
18565 Jamboree Road, Suite 250
Irvine, CA 92612-2565
949.989.8292
adykhuis@mwe.com

On behalf of the Defendant:
Cooley LLP
BY: JONATHAN DAVIES, ESQ.
BRITTANY CAZAKOFF, ESQ.
SANYA SUKDUANG, ESQ.
GABRIEL FERRANTE, ESQ.
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004
202.842-7889
Jdavies@cooley.com

Bradley Loy, Videographer

TABLE OF CONTENTS

EXHIBITS

P R O C E E D I N G S

THE VIDEOGRAPHER: We are now on the record. This begins videotape Number 1 in the deposition of Dr. Steven Nathan in the matter of United Therapeutics Corporation v. Liquidia Technology in the District Court of Delaware, Case No. 23-975.

Today is March 10, 2024. The time is 9:01. This deposition is being taken at 1900 N Street, NW, Washington, D.C., at the request of Cooley, LLC.

The videographer is Bradley Loy of Magna Legal Services, and the court reporter is Barbara Moore, Magna Legal Services.

Would counsel please state their appearances and who they represent.

ATTORNEY DAVIES: Jonathan Davies from Cooley for the defendant Liquidia, and with me today are my colleagues, Brittney Cazakoff and Sanya Sukduang.

ATTORNEY DYKHUIS: Art Dykhuis with McDermott Will & Emery for the plaintiff and the witness, Liquidia

Therapeutics. Also with me is Gabriel Ferrante.

****

STEVEN D. NATHAN, M.D.,

having been called as a witness on behalf of the Plaintiff and having been first duly sworn, was examined and testified as follows:

EXAMINATION BY
ATTORNEY DAVIES:

Q. Okay. Good morning, Dr. Nathan. How are you?
A. I'm good. How are you doing?
Q. Could you state your address for the record.
A. It's 1252 Cobble Pond Way, Vienna, Virginia, 22182.
Q. Have you been deposed before?
A. Yes, I have.
Q. About how many times?
A. It's in my declaration, but I believe it's three or four times.
Q. So today you understand you're under oath, and it's the same oath that you would be under if you were testifying in court; correct?
A. Yes.

Q. Okay. Today you're being recorded both by video and also stenographically, so we ask that you give verbal responses rather than just head nods or hand gestures.
Does that make sense?
A. Yes.
Q. I'll try to be clear with my questioning. If I'm not clear, you can ask me to clarify my questions, but if you provide an answer, I'll assume that you understood my questions.
Does that make sense?
A. Sounds good.
Q. Your counsel may object at various times today, but you understand that you still need to respond to my questions unless your counsel instructs you not to answer?
A. I understand.
Q. Okay. I'll take breaks, as we discussed, periodically. If you need a break, at any time, the only thing I ask is that if there's a pending question, you answer that question and we can take a break, okay?
A. I understand.
Q. Is there any reason why you can't provide truthful and accurate testimony today?

A. None.
Q. When was the first time that you were contacted by counsel for United Therapeutics about assisting in this matter?
A. It was sometime at the beginning of February.
Q. February of this year?
A. 2024, yes.
Q. And who contacted you?
A. I think it was a gentleman by the name of Adam Horowitz.
Q. When did you begin working on the declaration that you submitted in this case?
A. It was also sometime around the beginning of February.
Q. First week of February, do you think?
A. Approximately.
Q. And in preparing your declaration, what attorneys did you work with?
A. I worked with a bunch of different attorneys, some of whom are sitting here today, and the others I'm sure were involved as well.
Q. Did you work with Mr. Dykhuis on the case?

A. You know, I'm not sure if he was part of helping with the declaration, but I suspect he did.
Q. How generally was your declaration in this case prepared?
ATTORNEY DYKHUIS: Object to form and also just caution you, Dr. Nathan, don't divulge of substance of any communications with counsel, but you can describe generally.
THE WITNESS: It was a -- the declaration was formulated by myself together with assistance of the counsel.
BY ATTORNEY DAVIES:
Q. Do you recall any of the names of the counsel that assisted with the preparation?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There were a number of people on the email chain, and I'm not sure who exactly assisted. It seems like it was a combined effort on the part of counsel.
BY ATTORNEY DAVIES:
Q. Did you have any in-person meetings to prepare your declaration?

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A. No.
Q. Did you draft any portions of your declaration?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I did.
BY ATTORNEY DAVIES:
Q. Do you recall, sitting here today, which portions you drafted?
A. Most -- or if not all of the medical stuff is what I wrote, primarily.
(Exhibit 1 was marked for identification.)
Q. Dr. Nathan, I've marked as Exhibit 1 a deposition notice entitled Defendant Liquidia, Inc.'s Notice of Deposition of Steven D. Nathan. I'm going to pass that to you. I just ask you because of the weird shape of the table, would you mind passing one copy to counsel all the way around?
A. Sure.
Q. Thank you very much.
Doctor, you should keep the copy with the yellow stickers on it, if that makes sense.
A. Yes.
Q. And you understand that you're here

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today testifying in a case between United Therapeutics and Liquidia in which you submitted a declaration; correct?
A. Yes.
(Exhibit 2 was marked for identification.)
Q. So I've marked as Exhibit 2 a document titled "Declaration of Steven D. Nathan, M.D, in support of Plaintiff's motion for preliminary injunction."
And, again, I'm going to pass to you one extra copy if you can pass that to Mr. Dykhuis, please.
And Dr. Nathan, is Exhibit 2 that I just passed you, is that the copy of the declaration that you submitted in this case?
A. I just want to check to see what else is in there.
Yes, it is.
Q. This copy that I passed you to includes Attachments A, B, and C; correct? And they begin after page 90 of your declaration.
A. Attachment A? After 90? This is C at the end. I don't dispute it.
Q. Does this appear to be a complete

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copy of the report that you submitted in this case?
A. It does appears to be it.
Q. Could you turn to what would be page 90. It's the last page of your report before the attachments.
A. (Witness complies with request.)
Yes.
Q. And that's your signature on page 90?
A. Yes, it is.
Q. And it's dated February 26, 2024?
A. Yes.
Q. With respect to this declaration, are there any mistakes or errors in this declaration that you're aware of sitting here today?
A. There must be one or two typos that I saw subsequently. For example, an "and" instead of "an" and one of the footnotes there's also a typo.
Q. Could you point me to the footnote that's a typo.
A. Oh, gosh. Give me a minute. Okay. Sorry it's taking a while. I have a lot of documents to go through.

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I didn't see it in the first run. If I may, may I ask counsel to point me to where there's that footnote? Would that be okay, or do I have to keep looking?
Q. I would not object to asking your counsel which one it is.
ATTORNEY DYKHUIS: I think you might be thinking of Paragraph 119.
(Pause)
THE WITNESS: So that's page 43 you're talking about?
BY ATTORNEY DAVIES:
Q. Do you believe the error is in either footnotes 99, 100, or 101 on page 43, Doctor?
A. No, I think it's another footnote.
Q. Okay.
A. I apologize.
Q. Do you recall the nature of the error, Dr. Nathan?
A. It was just really a minor error --
Q. Okay.
A. -- that just had an incorrect reference to what the subject matter was. It wasn't really pertinent to anything, really. And

I'm not sure if we go through this if I might come across it as we go through.
Q. So other than an "and" rather than and "an" and a minor footnote -- a minor typo in a footnote, are there any other errors or typos that you're aware of in your report today?
A. None that I'm aware of.
Q. Okay. Can you go to Attachment B of your declaration, Exhibit 2.
A. (Witness complies with request.)
Q. Just let me know once you're there.
A. Attachment B is one page, and I see here that I had said four. I might be mistaken. There might have been one many, many years ago that wasn't picked up. I apologize if that is an oversight on my part.
Q. The one many, many years ago, was that a -- did you act as an expert in that case many, many years ago?
A. I believe so, yes.
Q. Okay. Did that case concern pulmonary hypertension?
A. I don't recall the details of the case.
Q. Do you recall if that was a patent

litigation case?
A. It was not a patent litigation case.
Q. Okay. What type of case was it, generally?
A. It was an medicolegal case.
Q. Like a med malpractice?
A. Yes.
Q. In the Genentech v. Aurobindo Pharma case, that's the first one in your prior testimony, did you author an expert report in that case?
A. I believe I did, yes.
Q. Were you deposed in that case?
A. As I recall, I was.
Q. Did you testify at trial in that case?
A. That I did, yes.
Q. And I'm not asking for confidential information, but can you tell me generally what the subject matter of your testimony was in that case?
A. It was regarding the validity of the patent over which the companies were having -- were contesting.
Q. And which of the parties were you consulting with?
A. I was consulting on behalf of

Genentech.
Q. So on behalf of the patentee?
A. That's correct.
ATTORNEY DYKHUIS: Object to form.
Q. Do you remember generally the subject matter of the patent at issue in that case?
A. I do.
Q. And what was it?
A. There were two clauses pertaining to checking liver function tests and another clause pertaining to drug-drug interactions.
Q. Is the Christopher -- the next case on your list, the Christopher Mee versus Robertson [sic], is that a medical malpractice case?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: It is.
BY ATTORNEY DAVIES:
Q. And the Washington verus American Homes, what type of case was that?
A. I don't recall exactly the details of that. It might have been, but I'm not sure, just by judging by the names, there was one case I was involved in where the -- I guess it would be the plaintiff had some exposure to chlorine. And

just by virtue of the names here, it might have been that one, but I'm not certain.
Q. So other than the four cases that we've talked about, any other cases that you've testified either by deposition or at trial that you can recall sitting here today?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: As I mentioned, there might have been another one way back, and I just don't remember the details of that. It wasn't patent litigation. It was not medical malpractice.
BY ATTORNEY DAVIES:
Q. Okay. Can you go, Doctor, to Exhibit A, please. I'm sorry, Attachment A of your declaration. Apologies.
A. Attachment A looks like my CV.
Q. Is this the most current copy of your CV?
A. I keep my CV updated as publications and talks come out. So my CV is updated, can be weekly, depending on what's going on. There haven't been substantive changes to my CV.
Q. Did you update this CV after being

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contacted by counsel for United Therapeutics in this case?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: As I say, I'm constantly updating it depending on what I'm doing. And so whenever I'm contacted to forward my CV, I forward the most recent copy of it.
BY ATTORNEY DAVIES:
Q. Do you recall, sitting here today, whether you updated it after being contacted by counsel for UTC regarding work in this case?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I do, because I know that I've had papers accepted or published. When I have a paper accepted or published, I'll go back to my CV and update it.
BY ATTORNEY DAVIES:
Q. This CV was updated in -- on January 17 of 2024. Is that right?
A. That's the date on the CV.
Q. Okay.
A. So that was -- whenever I was contacted, that was the last time I updated it, so

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this is the most current iteration of my CV when I was asked for it.
Q. So United Therapeutics would have contacted you before February 17, 2024?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Regarding this case do you mean?
BY ATTORNEY DAVIES:
Q. Correct, yes.
A. I don't recall being contacted previously by United Therapeutics.
Q. I apologize. I may have misheard your prior testimony, but I thought you said that you had updated this after being contacted by counsel for United Therapeutics.
ATTORNEY DYKHUIS: Object to form.
BY ATTORNEY DAVIES:
Q. For this case.
A. No.
Q. You did not.
A. I got contacted, to the best of my knowledge, at the beginning of February, Dr. Nathan, please send us your CV. I got back and I sent my CV. The last time I updated was on 1/17. So there might have been a two-week window where I

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had nothing to input to update it.
Q. Understood. Thank you.
Can you go to page 2, please, Dr. Nathan.
A. I'm on page 2.
Q. And it describes your postgraduate education at the top of the CV. Is that correct?
A. That's correct.
Q. Can you describe what you consider to be your areas of specialty with regard to medical practice?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: My areas of specialty would be pulmonary and critical as well as lung transplantation with subsequent initial expertise in interstitial lung disease, pulmonary hypertension, in other 25 of advanced lung disease.
BY ATTORNEY DAVIES:
Q. Doctor, I think you said "with subsequent initial expertise in interstitial lung disease and pulmonary hypertension."
A. Additional.
Q. Subsequent additional expertise.
Was that your testimony?

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A. Correct.
Q. Okay.
A. There's no formal training for those, but those are areas that I've gravitated towards.
Q. And when did you gain this subsequent additional expertise in interstitial lung disease and pulmonary hypertension?
A. It's accrued over the years. There's no formal training for interstitial lung disease and pulmonary hypertension, at least that wasn't in my day.
But I've been involved in pulmonary hypertension since my fellowship at Cedar Sinai, which was the referral center for patients with primary pulmonary hypertension at that time. So I've been seeing patients with pulmonary hypertension since the start of my fellowship, which was in 1988, if not before. I did see some cases as well as a resident.
Q. Are you currently employed?
A. Yes, I am.
Q. And where are you currently employed?
A. I'm employed at Inova Fairfax

Hospital.
Q. And what is your position at Inova?
A. I'm the medical director of the advanced lung disease and lung transplant program.
Q. In your CV it identifies a medical director position at Inova Fairfax that began in May 2018.
Do you see that?
A. Yes.
Q. Okay. And then it says "inactive."
A. Yes.
Q. What does "inactive" mean in your CV?
A. Inova has gone through various iterations of how they want to organize pulmonary. And initially the pulmonary service line asked us to direct, to reorganize. And so the service line concept went away.
Q. Do you have any academic positions other than your employment at Inova Fairfax?
A. I have an employment as professor of medical education at University of Virginia.
Q. Any other academic appointments?
A. Not at this time.
Q. Any other employers other than Inova

Fairfax currently?
A. No.
Q. It also has a position as a professor of medical education at the University of Virginia. Are you still involved with that?
A. Yeah, that's the appointment that I just mentioned.
Q. Okay. There is also a professional professor of medicine position at Virginia Commonwealth University.
A. Yes.
Q. Are they two positions, or are they the same thing?
A. That probably should read as ended, because what happened was that Inova has affiliations with VCU Medical School, and at that time I was professor of medicine at VCU. And then they changed their medical school affiliation to UVA, and that's when I got the subsequent appointment.
So effectively -- and I apologize, it's very hard to keep everything up to date -- that that should have ended at the same time that the UVA appointment started.
Q. My CV is about four pages long, and

I don't even keep that accurate so I have no doubt that it's more difficult for you to do so.
In your current position at Inova, can you describe to me generally your responsibilities in that position.
A. I oversee the advanced lung disease and lung transplant program. In the context of their advanced lung disease program, we had various other programs, including a pulmonary hypertension program, which is accredited by the Pulmonary Hypertension Association as one of the care centers.
We have an interstitial lung disease program that's accredited by the Pulmonary Fibrosis Foundation. We have a cystic fibrosis program that's accredited by the CF Foundation, and we have a comprehension saccharidosis program, that's accredited by the World's Association for Saccharidosis and Other Granulomatous Diseases.
Q. Do you still -- maybe I used the wrong word there.
Do you still see patients in the clinic?
A. Yes, I do.
Q. Okay. And how many days a week are you working in the clinic seeing patients?

A. I work -- I work 10 and a half days in the clinic seeing patients, but then sometimes I'll add patients on if they need to be seen on an emergency or I want to squeeze them in, I might see them on a day that I'm not in the clinic.
Q. And is that split with your clinical practice, has that been true since about 2018?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's approximately correct. I don't remember exactly when I went to 2.5 or what effectively works out at a .5 clinical FD. I don't recall exactly when that was.
BY ATTORNEY DAVIES:
Q. How many pulmonary hypertension patients are currently under your care?
A. Since it follows, in the range of about 400 to 500 patients with group 1 pulmonary arterial hypertension. And then we have approximately 11 to 1200 patients with interstitial lung disease, many of whom have pulmonary hypertension associated with interstitial lung disease.
There are a number of providers, but I see a good proportion of patients with pulmonary

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arterial hypertension, patients with interstitial lung disease and patient with IOVPH.
Q. Can you go to page 5 of your CV.
A. (Witness complies with request.) I'm on page 5.
Q. And it looks like it actually begins on page 4, there's a heading entitled "Committees." Do you see that?
A. Yes.
Q. And it appears to include your membership on steering committees for various clinical studies. Is that correct?
A. That's correct.
Q. If you go to the top of page 5, there's a study, the very first one, 2016 to 2021, steering committee member of phase 2B study of Sildenafil added to pirfenidone in advanced IPF in an immediate or high probability of Group 3 PH. Do you see that?
A. I do.
Q. Do you recall the study name?
A. There was an acronym that went with it. I don't recall what that acronym was.
Q. Was there a publication that issued from that study?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, it was. I believe it was published in the Advanced Respiratory Medicine.
BY ATTORNEY DAVIES:
Q. Were you one of the authors on that paper?
A. As I recall, I was the second author on that paper.
Q. Do you recall generally the outcome of that study?
A. The study was a negative study.
Q. In what sense was it a negative study?
A. It didn't meet its primary endpoint.
Q. What was the primary endpoint?
A. As I recall, it was time to clinical worsening.
(Reporter clarification)
Q. Were there any other primary endpoints?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There were -- not at the primary endpoints. Typically in the studies you only have one primary

endpoint. On rare occasions there could be two primary endpoints.
BY ATTORNEY DAVIES:
Q. If you go down -- I'll find it. If you go down to the next -- I'm sorry. If you go down to the next entry, there's a steering committee member for RIN PH 201, the INCREASE study. Do you see that?
A. I do.
Q. Okay. When was the steering committee formed for INCREASE?
A. Based on my CV, it appeared that it was in 2016.
Q. So that indicates the beginning of your involvement as a steering committee member?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Based on my CV, I believe that would be correct.
BY ATTORNEY DAVIES:
Q. Who else was a member of the steering committee for INCREASE?
A. There were two other members: Dr. Aaron Waxman and Dr. Richard Tapson.
Q. Can you repeat the second member of

the steering committee for INCREASE, Doctor.
A. Victor Tapson.
Q. Victor Tapson?
A. Yes.
Q. What was the responsibility of the steering committee with respect to the design of the INCREASE?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We were all involved in coming up with the design in terms of inclusion, exclusionary criteria, and endpoints, as I best recall.
BY ATTORNEY DAVIES:
Q. What was your contribution, in your view, to the design of the INCREASE study?
A. I don't remember my individual contribution. We're talking, I guess, nine years ago now. I'm sure that I had some kind of contribution, and at the end of the day it was a consensus in terms of how the study was designed.
Q. Other than the three steering committee members, did anyone else have involvement in the study design of the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, there were.

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There were representatives from United Therapeutics. It was their study, and Peter Smith was one of them. C.Q. Quinn, who was the biostatistician, was also involved in terms of figuring out how we're going to analyze the data statistically.
BY ATTORNEY DAVIES:
Q. Anyone else you recall?
A. I don't remember. I made a mistake. I said nine years ago. My math was incorrect. It's eight years ago.
Q. No problem. We all get grades today because we lost an hour last night.
A. We lost what?
Q. We lost an hour last night.
A. I thought you were going to say that you were a Duke fan.
Q. Do you recall anything about Dr. Aaron Waxman's contribution to the design of the INCREASE study?
A. I do not.
Q. Do you recall anything about Dr. Victor Tapson's contribution to the design of the INCREASE study?

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A. I do not. As I said, we've all contributed in our own way, and then the study design ultimately was a consensus against everyone, including the folks from United Therapeutics.
Q. Okay. There's no end date for the steering committee membership for the INCREASE study in your CV. Is that steering committee still active?
A. We don't meet as a steering committee. However, where there is activity are various post hoc analyses of the INCREASE study which remain ongoing, and that's probably the reason that I haven't closed it out.
Q. Are there any current post hoc analyses of INCREASE that are ongoing?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, they there.
BY ATTORNEY DAVIES:
Q. And what are they?
A. We've done numerous post hoc analyses. There's one paper that's in submission about treating patients with more mild pulmonary hypertension as the subject of analysis.
There is another paper being developed pertaining to a risk score in terms of the patients

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who were enrolled in the INCREASE study.
Q. You said it's corresponding to a risk score?
A. Risk score. Risk stratify the patients who have pulmonary hypertension who were in the study.
Q. Are there any post hoc analyses concerning FVC?
A. There was one that was published in Advanced Respiratory Medicine.
Q. Are you an author on that paper?
A. Yes.
Q. Why was there a post hoc analysis of the INCREASE study done with respect to FVC?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The FVC looked at -- at baseline and then at the end of the study, and what we saw appeared to be a difference favoring inhaled treprostinil in terms of preservation of the FVC in comparison to the placebo arm, and that was the basis for the post hoc analysis.
BY ATTORNEY DAVIES:
Q. So with respect to the initial INCREASE study, you said you saw what appeared to

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be a difference; is that correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Correct.
BY ATTORNEY DAVIES:
Q. Was in your opinion -- with the initial analysis of INCREASE, was there a statistically significant difference in FVC with inhaled treprostinil treatment?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: As best I recall, there was based on percent predicted, but not absolute in terms of milliliters. However, those became significant when we looked at various subgroups, including those patients with idiopathic interstitial pneumonia and a further subgroup of those patients, the patients with idiopathic pulmonary fibrosis.
BY ATTORNEY DAVIES:
Q. So at least with the initial INCREASE study, there was not a significant difference in FVC with treprostinil treatment across all patients; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There was. There

are two ways you can look at the FVC.
You can look at the absolute number, which is how many ccs or milliliters, or you can look at it as a percent predicted, and there was a statistical difference when you looked at it based on percent predicted.
BY ATTORNEY DAVIES:
Q. Which of those two measures or analyses do you feel is more accurate?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: They are both accurate. They just tell you different ways of looking at the FVC.
BY ATTORNEY DAVIES:
Q. What's the significance to you as a clinician where one method produces a statistically significant difference and the other does not?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It really doesn't make a difference to me how I look at the data, to be quite honest.
BY ATTORNEY DAVIES:
Q. What do you mean, it doesn't make a difference to you how you look at the data?

A. I look at the compendium of the data. One is positive, one is negative. I wouldn't say "negative." It probably was a trend; I don't remember what the P value was. But the study wasn't powered to look at the FVC.
So it's an interesting observation that remained to be further validated and that is currently ongoing.
Q. Was the post hoc analysis powered to look at FVC?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: No, you can't power a study retrospectively.
BY ATTORNEY DAVIES:
Q. Why -- whose decision was it to do the post hoc analysis for FVC?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It was an easy group decision, because we saw the signal when we looked at the FVC, and it was somewhat surprising and unexpected.
FVC was initially looked at as a safety measure. We're giving a medication by the inhaled drug to

patients who had interstitial lung disease, and we didn't know if we would be hurting these patients because they are very different from Group 1 PAH patients that have parenchymal lung disease and getting anything inhaled is the possibility you could harm them. And that was why it was labeled as a safety endpoint.
BY ATTORNEY DAVIES:
Q. Sitting here today, are you confident that administration of inhaled treprostinil produced a statistically significant improvement in FVC in the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: If you look at percent predicted, I'd have to go to the paper, if you have it, just to make sure what I'm saying is the truth. But as best I recall, there was a statistically significant difference. So I'm confident with that.
I would need to look at the paper to make sure that what I'm telling you is correct, but that's the best of my

recollection. So I'm confident in the analyses that were done in the post hoc analysis.
BY ATTORNEY DAVIES:
Q. And what about the initial analyses in the absence of the post hoc analyses? In your opinion, does that support a statistically significant improvement in FVC, or was it uncertain with the initial analysis?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I believe the initial analysis showed the same thing. It's just that in the post hoc analysis we dug deeper into it, and that's when we did the subgroup analyses.
BY ATTORNEY DAVIES:
Q. So to the best of your recollection, with respect to FVC, INCREASE showed a significant difference in percent predicted. Is that correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: In favor of inhaled trepostinil versus placebo.
BY ATTORNEY DAVIES:
Q. Is that correct?
A. Correct.

Q. But with respect to absolute improvements in FVC, there was not a significant difference following treatment with inhaled treprostinil in the INCREASE study; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I wouldn't regard it as improvement. I believe that's what you said. It was placebo-corrected difference.
BY ATTORNEY DAVIES:
Q. So there was not a significant difference in absolute FVC in the INCREASE study; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's to the best of my recollection.
BY ATTORNEY DAVIES:
Q. Okay.
A. For the patients as a whole, but for the subgroups it was.
Q. When was the -- when was the post hoc analysis on FVC, when was that started?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't recall the exact date. I think that it was probably

2021 sometime, early 2021, but I don't recall the exact date. Sorry.
BY ATTORNEY DAVIES:
Q. No problem.
You mentioned that the INCREASE study was designed by a consensus of the five committee members that you can recall; correct?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It was the three steering committee members and the sponsor.
BY ATTORNEY DAVIES:
Q. Okay. And the protocol for INCREASE was designed as a consensus of the three committee members; is that correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Together with the sponsor.
BY ATTORNEY DAVIES:
Q. Okay. Do you remember any input that the sponsor offered UTC -- strike that. Let me start over.
Can you recall sitting here today any specific -- let me try it one more time.

Sitting here today, can you recall any specific input or contribution of United Therapeutics's representatives to the design of the INCREASE study?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: They had a substantial contribution. The way it worked is that we were sent a cursory protocol, and then we provided input in terms of, you know, maybe think about this, maybe think about that, but they really provided the foundation for the study.
BY ATTORNEY DAVIES:
Q. Do you recall sitting here today any belief by the study members -- strike that.
Do you recall sitting here today any belief by the steering committee members that the study would not be successful?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: Yes. I had my doubts that it would be successful for sure.

BY ATTORNEY DAVIES:
Q. Why did you believe it would not -- well, why did you have doubts regarding the success of the study?
A. Because it had been no prior randomized controlled study in PH-ILD demonstrating success, and personally I had just come off being the chair of the steering committee of the RISE IP study, which was riociquat for the same indication, PH-ILD, and not only was that a negative study, but it was a harmful study.
Q. Do you recall Dr. Waxman expressing any belief that the study would not be successful?
ATTORNEY DYKHUIS: Objection, form.
THE WITNESS: I don't recall that.
BY ATTORNEY DAVIES:
Q. Okay. Do you recall Dr. Victor Tapson expressing any belief that the study would not be successful?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: I don't recall that.
BY ATTORNEY DAVIES:
Q. Okay. Regarding your feelings about

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the study in your past experience from the RISE study, why were you willing to be a member of the steering committee, given your past experience with RISE?

ATTORNEY DYKHUIS: Objection to the form.

THE WITNESS: I was asked to be a steering committee member, and I valued the opportunity. And we have many negative studies in medicine that have subsequently been followed by positive studies.

So I think the history of medicine is such that if you have one negative study, you don't necessarily give up. If you look at another disease that I deal with, idiopathic pulmonary fibrosis, for which there are two anti-fibrotics that are approved, there are about 10 RCTs, randomized studies, prior to that before those came back positive.

So, you know, if we just gave up on all treatments, we wouldn't have anything for cancer today.

BY ATTORNEY DAVIES:

Q. So when during the development of the INCREASE study did you become optimistic that it would succeed?

ATTORNEY DYKHUIS: Object to the form.

THE WITNESS: When I heard the results.

BY ATTORNEY DAVIES:

Q. So until you heard the results of the INCREASE study, you were not optimistic that the study would succeed?

ATTORNEY DYKHUIS: Object to the form.

THE WITNESS: I had my doubts.

BY ATTORNEY DAVIES:

Q. And when did you first hear the results of the INCREASE study?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: It was sometime towards the end of February of 2020.

BY ATTORNEY DAVIES:

Q. Do you recall who communicated those results to you?

A. Peter Smith.

Q. Who is Peter Smith?

A. He was one of the two UT members, and he led the study from the sponsor standpoint for United Therapeutics.

Q. Do you recall United Therapeutics ever expressing any skepticism that the INCREASE study would not be successful?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: No.

BY ATTORNEY DAVIES:

Q. The communication in February 2020 that you received from Peter Smith regarding the data, was the study data locked at that point, or what stage in data collection was ongoing at that point?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: The study was locked, and they had done the analysis of the primary endpoint, and I believe at that time some of the secondary endpoints as well.

BY ATTORNEY DAVIES:

Q. So by the time you got -- you heard the results from Peter Smith, the study had been locked and there had been analysis on both the primary and secondary endpoints as well; correct?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: As best I recall.

BY ATTORNEY DAVIES:

Q. And this was the first time that you were optimistic that the study would be successful; correct?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: That's correct.

BY ATTORNEY DAVIES:

Q. Did Leigh Peterson contribute to the design or conduct of the INCREASE study?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I don't recall specifically that she could well have. I suspect that there was a lot of communication behind the scenes that the steering committee members were not necessarily privy to.

BY ATTORNEY DAVIES:
Q. To your knowledge, who is Leigh Peterson?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: She's an employee of United Therapeutics.
BY ATTORNEY DAVIES:
Q. Do you know generally what her responsibilities were, if any, with respect to the INCREASE study?
A. I do not.
Q. Did you ever have any conversations with Leigh Peterson regarding the INCREASE study?
A. I don't recall any.
Q. Do you know if Peter Smith had any contribution to the design or conduct of the INCREASE study?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: I'm pretty sure he did without knowing a hundred percent. He led the study, so I think it's reasonable to assume that he had some essential contributions, but I can't tell you for sure.

BY ATTORNEY DAVIES:
Q. What about Chung Kun Dang? Did he have any role in the conduct or design of the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, he did, because he's the biostatistician that helps to come up with the statistical analysis plan.
BY ATTORNEY DAVIES:
Q. Below -- going back to your CV, Doctor, I'm sorry, your CV is Attachment A to your declaration, which is Exhibit 2.
The next steering committee membership I wanted to ask you about began in 2016, steering committee member for RIN PH 203 study.
Do you see that?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: Yes, I do.
BY ATTORNEY DAVIES:
Q. Does that have a study name?
A. Yes, it does. That is known as the PERFECT study.
Q. Who else was on the steering

committee for the PERFECT study?
A. It was myself, Vic Tapson -- Victor Tapson, Aaron Tapson, and there was an additional member, Todd Bull, B-u-l-l.
Q. And is that steering committee still active as well?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: The paper pertaining to that study is currently in development, and so with regards to fine-tuning the paper, the steering committee still has input into that.
The study got stopped early for lack of efficacy and a signal of potential harm, and this was inhaled treprostinil in patients, with COPD.
BY ATTORNEY DAVIES:
Q. Is PH due to COPD, is that a Group 3?
A. That's correct.
ATTORNEY DYKHUIS: Object to the form.
Q. I'm sorry. I want to just ask, I'll try to rephrase that a little bit better.

Is pulmonary hypertension due to chronic obstructive -- strike that.
How many -- you're aware that there's five groups of pulmonary hypertension; correct?
A. That's correct.
Q. Okay. Which of those five groups does pulmonary hypertension due to chronic obstructive pulmonary disease fall into?
A. Group 3.
Q. Do you know whether United Therapeutics was still investigating the use of inhaled treprostinil for PH COPD?
A. I don't believe they are.
Q. Why do you believe that that study failed?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I don't know why the study failed. There are many moving parts to a successful study design. I think it just underscores a point that not all forms of lung disease which are conflicted by pulmonary hypertension necessarily behave the same or respond the same to therapy.

BY ATTORNEY DAVIES:
Q. If you turn to page 8, there's a list of your publications that begins on page 8.
A. Okay.
Q. And I believe you testified that you're not aware of any significant additions to that list of publications.
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There have been some publications that have been added. Maybe one or two. I can't recall exactly right now.
BY ATTORNEY DAVIES:
Q. Are there any that you're aware of that are or that concern the use of treprostinil?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'll have to go and see what the last entry is here.
No, I don't believe -- let me just double-check, I apologize. I don't believe that there are any new publications pertaining to inhaled -- trepostinil.
BY ATTORNEY DAVIES:
Q. If you turn to page 29 of your CV,

and this appears to be a list of publications in submission or preparation. Is that correct?
A. Correct.
ATTORNEY DYKHUIS: Object to form.
Q. We talked about the post hoc analysis with regard to FVC that was done for the INCREASE study.
Do you recall that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. Is 18 the in-preparation publication of those results and analysis?
A. No. This isn't the FVC. That was the question you had.
Q. Correct.
A. I can direct you to that one, because that's not in preparation. That has been published.
It's publication number 137.
Q. What is the post hoc analysis of INCREASE that's described at 18 on page 29 of your CV?
A. There's no mention of efficacy that I can see in Number 18.

Q. And I'm sorry, Doctor, I may not have been clear. What is the post hoc analysis of INCREASE that's described at Number 18 on page 29 of your CV?
A. That was looking at outcomes in patients with less severe pulmonary hypertension. It didn't pertain to the FVC.
Q. And why did you decide to do this post hoc analysis that's described in 18?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There have been many ideas that have come out with this very rich dataset, and that was one of them. Despite the overwhelmingly positive results, that does still exist in the community skepticism around the INCREASE study, and specifically with enough patients with more mild pulmonary hypertension are responders.
And that was a reason to do an analysis into patients who had more mild pulmonary hypertension just to drill down on all the potential benefits that you could see with if patients with mild pulmonary hypertension were treated.

BY ATTORNEY DAVIES:
Q. And what were the results of that post hoc analysis with respect to this more mild PH patient population?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Once you do post hoc analyses, the numbers get smaller. And when the numbers get smaller, it becomes much more difficult to show statistical significance.
But the point estimates in what we call the hazard ratios for clinical worsening did appear to favor inhaled trepostinil, as well as the point estimate for the risk of acute exacerbations did fail to -- I'm sorry, did favor inhaled trepostinil. It didn't reach statistical significance, and then the change in the biomarker were used, which is called the NT-ProBNP also showed a favorable effect in the group that got inhaled treprostinil. And I think the NT-ProBNP hits statistical significance.
BY ATTORNEY DAVIES:
Q. Did you examine change in six-minute

walk distance analysis in this post hoc analysis?
A. The change in the six-minute walk distance had been reported in the primary INCREASE publication in patients with more mild pulmonary hypertension. Honestly, I don't recall how much we reported out on the six-minute walk in this post hoc analysis. I think we did.
The paper is still in revision at the moment, but without having the paper in front of me, I can't tell you a hundred percent. I'm pretty sure that we must have examined the six minute walk distance.
Q. Do you recall whether there was a statistically significant difference in six-minute walk distance in this patient population subgroup with more mild pulmonary hypertension?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Well, if you go back to the primary paper, in the supplement to the primary paper there's an analysis of patients with pulmonary vascular resistances between three and four, and it did not appear to be any effect on the six-minute walk.
Hence, the skepticism, and hence

the reason we did this deeper dive looking at these other outcome measures which did appear to show benefit in this group of patients.
BY ATTORNEY DAVIES:
Q. You mentioned, I believe, in one of your earlier responses, Doctor, exacerbations of interstitial lung disease.
Did I recall that correctly?
A. Yes.
Q. What is an exacerbation of interstitial lung disease?
A. There's a strict definition for what an exacerbation of interstitial lung disease is and the guidelines for that in terms of worsening infiltrates on chest imaging, worsening shortness of breath over a time period of less than four weeks. Worsening gas exchange and ruling out other causes like infection or heart failure.
So it's -- and then if you rule all those out, you're left with an acute exacerbation of interstitial lung disease.
Q. With respect to this more mild PH subgroup of patients, was there a statistically significant difference with respect to

exacerbations of interstitial lung disease?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The points estimate was way to the left favorable for inhaled trepostinil. I think that it was something like an 80 percent risk reduction, if I recall the point estimate exactly. Because the numbers were very small, the error bars were very wide and crossed the line of unity so that the post hoc analysis suffered from insufficient numbers to have a definitive answer that the point estimate suggested strongly that there was a substantial benefit.
BY ATTORNEY DAVIES:
Q. But there was not a statistically significant difference; correct?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Because of the small numbers, that's correct, yes.
BY ATTORNEY DAVIES:
Q. With regard to the entire patient population within the INCREASE study, was there a

statistically significant difference in exacerbations of interstitial lung diseases on treatment with inhaled trepostinil?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I believe that there was.
BY ATTORNEY DAVIES:
Q. Why do you believe there was an effect seen in the larger patient population but not in the subgroup of more mild PH patients with respect to an effect on exacerbations in ILD?
ATTORNEY DYKHUIS: Objection. Form.
THE WITNESS: It's purely because of the numbers. We had, as I recall, 336 patients in the group as a whole, and then those who had mild PH -- I don't remember what the number was, it was 60 to 80 -- and once you have smaller numbers, it becomes much more difficult to hit statistical significance.
BY ATTORNEY DAVIES:
Q. Going back to your CV on page 29 -- and just let me know when you're back there -- there's an entry Number 24.

Do you see that?
A. I do.
Q. And it refers to a derivation of a simple risk calculator for predicting clinical worsening in patients with pulmonary hypertension due to interstitial lung disease.
Do you see that?
A. I do.
Q. And what does that paper describe, generally?
A. That's the paper that I mentioned earlier that's still in development, looking at all the patients from an INCREASE study and looking at their baseline characteristics to see if we can identify a high-risk group versus a lower risk group, a group of patients who are generally pretty high risk.
Q. And what do you mean by "high risk"?
A. For having an event like mortality, hospitalization, being events that are notable or sometimes you put that in a compass endpoint of clinical worsening. So that risk of having a bad outcome or higher risk of having a bad outcome.
Q. Is that risk based on treatment with inhaled treprostinil, or is that just they're high

risk due to their disease generally?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: High risk due to their disease generally. I believe the way we're doing it is we're just looking at the placebo arm to rule out the effect of inhaled trepostinil on their own interests.
BY ATTORNEY DAVIES:
Q. Other than your work in this case, are you consulting with United Therapeutics in any other matter?
A. I do consult with them in other matters, you know, depending on what's going on. You know, they have a working group, for example, that talks about PH-ILD, and I'm part of that working group. I'm on their speakers bureau.
So are there other ways in which I collaborate with United Therapeutics.
Q. Other than being on the working group with PH-ILD and the speakers group, how else do you collaborate with United Therapeutics?
A. I'm the chair of the steering committee for the Teton study.
Q. Anything else?

A. Not that springs to mind at the moment.
Q. Have you received funding as research grants from United Therapeutics?
A. Yes, I have.
Q. Do you have any sense for the amount of money that you received in research grants from United Therapeutics over the years?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't have a good sense.
BY ATTORNEY DAVIES:
Q. Is it more than $100,000?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I didn't get any money from them for research. It goes to my institution.
BY ATTORNEY DAVIES:
Q. Do you personally receive any other grants from United Therapeutics which aren't for research purposes?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No.
BY ATTORNEY DAVIES:
Q. Can you turn to page 44 of your CV.

A. (Witness complies with request.)
Q. This is in a section -- I'm sorry. Are you there, Doctor?
A. I am there, yes.
Q. Okay. And if you flip over a page or two, this is in a section of your CV titled "Research Grants, Pharmaceutical Multicenter Studies."
Do you see that?
A. Yes.
Q. Can you look at entry Number 31 on page 44.
A. (Witness complies with request.)
Q. Are you there?
A. Yeah.
Q. What was your involvement in the protocol for the LTI-301 study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I wasn't involved in this protocol development. As I recall, we were asked to be a center, and Moreau [phon.] was the subinvestigator. I wasn't even the principal investigator on that.

BY ATTORNEY DAVIES:
Q. What was your role as a subinvestigator in the study?
A. The fact that I was a subinvestigator just enabled me to see patients when they come in for study limits. Nothing more than that in terms of data analysis or anything else.
Q. Are you familiar with -- well, as your role as a subinvestigator and seeing patients as they came in, you've seen the dry powder inhaler that's used for administration of Yutrepia; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I haven't seen the Yutrepia device.
BY ATTORNEY DAVIES:
Q. Do you know what the Yutrepia device is?
A. I don't have a good idea what the device is.
Q. You do not?
A. I do not. I might have seen a picture of it, but I've never held one in my hands, no.

Q. Were you familiar with a Plastiape inhaler, that's RS00 Model 8?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't believe I am.
BY ATTORNEY DAVIES:
Q. Okay. So when patients came in as part of the LTI-301 study, what was your role as a subinvestigator when those patients came in?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: To be honest, I don't even remember seeing any of these patients. I might have been a sub-I on the protocol that we submitted without ever having seen one of these patients.
BY ATTORNEY DAVIES:
Q. When is the first time that you can recall hearing about Yutrepia or LIQ-861?
A. It's actually interesting, if I may. When you pointed me to this, I wasn't even aware that this was Liquidia's product. That's how much I recall about this study. I was very peripheral, and I've never saw any of these patients, and I never saw the device.
I was just listed as a sub-I at the start

of the study, as were a bunch of our associates. The reason we do that is in case a PI is not available, someone can substitute for them and see a patient, but that never happened to me.
Q. Do you know who the PI was at your institution for this?
A. I believe it was Dr. Oxanna Slobin.
Q. We've been going for about an hour. Do you want take a break?
A. I'm good. We can carry on unless you need to take a break.
ATTORNEY DAVIES: I need to take a break, so if you don't mind, let's take a quick break.
THE VIDEOGRAPHER: We are off the record at 10:12.
(Recess taken from 10:12 a.m. to 10:21 a.m.)
THE VIDEOGRAPHER: We are on the record at 10:21.
BY ATTORNEY DAVIES:
Q. Welcome back, Doctor. Thank you for accommodating my request for a break, I appreciate that.
You mentioned earlier this morning an

initial protocol for the INCREASE study.
Do you recall that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We did talk about the INCREASE study and how it was formulated, yes.
BY ATTORNEY DAVIES:
Q. And I believe you testified that there had been a draft of a protocol that was provided from United Therapeutics, and you commented and had input on that; is that correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.
BY ATTORNEY DAVIES:
Q. Do you know what the basis or rationale was for the INCREASE protocol draft from United Therapeutics?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The premise was to give inhaled treprostinil and to see if it would be of benefit in patients with pulmonary hypertension associated with -- interstitial lung disease.
BY ATTORNEY DAVIES:
Q. Are you aware of whether it relied

on any results from prior studies to support in the design of the INCREASE protocol?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm not aware of, you know, the studies, I'm sure the studies looked at all the studies in the literature prior to that, but I don't know of anyone that they leaned on.
BY ATTORNEY DAVIES:
Q. Can you go back to the beginning of your declaration, which is Exhibit 2. And if you go to the table of contents for your declaration, just let me know when you're there.
A. (Witness complies with request.) Yes.
Q. You mentioned that you drafted the medical portions of your declaration. Can you identify the portions of your declaration in the table of contents that you prepared?
ATTORNEY DYKHUIS: Object to form.
I would say that I -- all portions I had input on. I might have not been the first draftee, but, you know, the legalese stuff, there was the foundation provided by counsel and, certainly if

there was anything that I didn't understand it was explained to me. So it was a lot of wordsmithing that went around that.
But if we go through the medical stuff, I know that -- I think it's just about 58 points looks like it's more legal stuff.
BY ATTORNEY DAVIES:
Q. When you said "points," Doctor, you're referring to the first 58 paragraphs or more of legal stuff that you didn't prepare?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I wouldn't say I didn't prepare it. I didn't prepare necessarily the first draft, but then I had input subsequently of the things that I didn't understand; they were laid out differently and I might have done some wordsmithing myself amongst all the different paragraphs. I don't recall exactly what.
But if you look at from Scientific Background, 59, 68, 69, 70, I believe counsel helped put this table together.

I think I provided the names of the drugs, if I recall correctly.
Seventy-three, 74, this all looks medical. Seventy-five, 76, 77, and then all prior studies, I wrote that. I think counsel was aware of some of these studies and might have mentioned it, but I really provided the verbiage that I went through with each of these studies. RISE IP, Sildenafil, pirfenidone, we spoke about that.
The PERFECT study was mentioned. I don't know if you wanted me to make my way through the whole document and pick out areas that I was involved in. The INCREASE study, I believe that I was a primary person who wrote that.
But then when you come to areas like patent, you know, that's where counsel helped to lay out the initial foundation in terms of the first draft.
BY ATTORNEY DAVIES:
Q. There's reference on page 36 to the prosecution history of the '327 patent.
A. Yeah.

Q. What is the prosecution history of the '327 patent?
A. It's kind of a dying --
ATTORNEY DYKHUIS: Object to form. Sorry, give me a moment to make any objections.
THE WITNESS: I'm sorry.
ATTORNEY DYKHUIS: The other thing I would say, Dr. Nathan, in this line of questioning just a reminder I caution you not to reveal of substance of any communications with counsel, but you can explain.
THE WITNESS: Thank you.
To my understanding, the prosecution history is going backwards and forwards between the courts in terms of the lawsuit is brought and it's revised and then the decision and then you've got a counterclaim or whatever. So that's how it's being prosecuted historically.
BY ATTORNEY DAVIES:
Q. Do you recall reviewing the prosecution history of the '327 patent in terms of

preparing your report?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I did.
BY ATTORNEY DAVIES:
Q. You did.
Can you go to page 43.
A. (Witness complies with request.)
Q. And there's a section of your report here entitled, "Liquidia will infringe the asserted claims of the '327 patent."
Do you see that?
A. I do.
Q. Did you prepare this section of the report on the infringement of the claims of the '327 report, or is this legal opinion?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It's my opinion.
BY ATTORNEY DAVIES:
Q. Did you prepare any portions of those, or did counsel prepare them?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Honestly, I can't remember who contributed what to this first draft. It might well have been counsel because I wasn't familiar which

claims were being contested, but I certainly had input into this.
BY ATTORNEY DAVIES:
Q. We talked a little bit about statistical significance in a couple of different context earlier this morning.
Do you recall that?
A. Yes.
Q. Is it possible to determine whether there has been a statistically significant difference within a single patient with respect to a treatment?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No.
BY ATTORNEY DAVIES:
Q. Why not?
A. You need --
ATTORNEY DYKHUIS: Sorry, object to form.
THE WITNESS: You need a large study to determine the statistical significant. There's a lot of things that can happen by chance in an individual patient, which if under treatment may or may not be attributable

to the treatment. So you can't determine statistical significance in a single patient.
BY ATTORNEY DAVIES:
Q. Just to make it clear, and I don't think you heard me correctly, but I believe your testimony was that you cannot determine whether there is a statistically significant difference in a patient with respect to a treatment; correct?
A. Correct.
ATTORNEY DYKHUIS: Object to form.
Just while there's a pause again, Doctor, just give me a moment to get in any objections.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. We've talked about pulmonary hypertension. What in your -- what in your words is pulmonary hypertension, Doctor?
A. Pulmonary hypertension is a build-up of pressure in the pulmonary arterial circulation.
Q. And how do you diagnose a patient with pulmonary hypertension in your practice?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The diagnosis always

relies on a right heart catheterization to analyze the pressures.
BY ATTORNEY DAVIES:
Q. And what pressures from that right heart catheterization would indicate to you as a clinician there is pulmonary hypertension present?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It depends which definition you're talking about, because there have been a lot of changes to the definition.
When the INCREASE study was undertaken, we used what is known, an older definition of a mean pulmonary artery pressure of 25 milliliters or more accompanied by pulmonary vascular resistance of three or more wood units.
That definition was subsequently changed at the Sixth World Symposium in 2018, and the mean pulmonary artery pressure was lowered to greater than 20 milliliters of mercury with the pulmonary vascular resistance remaining the same at three or more wood units.
More recently, the European

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Society of Cardiology and the European Respiratory Society came up with another new division -- sorry, definition, where they kept the mean pulmonary artery pressure the same, greater than 20 milliliters of mercury but decided to take the pulmonary vascular resistance halfway down to two.

So based on the ESCERS guidelines from 2022, the current definition is a mean pulmonary artery pressure of 20 or more milliliters of mercury accompanied by a pulmonary vascular resistance of greater than two wood units.

BY ATTORNEY DAVIES:

Q. And what was the definition that you would have applied as of April 2020 with respect to pulmonary hypertension?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: In 2020, we had the definition from the World Symposium in 2018. But 2020 was the time that the INCREASE study results came out, which was formulated under the guise of the old definition.

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So what I would regard as hypertension -- let me back up a little bit.

Pulmonary hypertension is defined by a mean pulmonary artery pressure of greater than 20 milliliters of mercury. You're talking about precapillary pulmonary hypertension, then you need the pulmonary vascular resistance component of it.

So in 2020 what I would regard as pulmonary hypertension would be a mean pulmonary artery pressure of 20 or more milliliters of mercury.

However, with regards to putting patients on inhaled treprostinil, we have to revert to the old definition because we only know that the drug works in that population of patients in the study.

BY ATTORNEY DAVIES:

Q. So you're saying the INCREASE study applied a different definition of PH, which is more narrow than the definition that existed in 2020; is that correct?

ATTORNEY DYKHUIS: Object to the form.

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THE WITNESS: That's true. It's not by designed. The INCREASE study was implemented and undertaken when we were all functioning under the guise of the old definition.

BY ATTORNEY DAVIES:

Q. We had talked earlier about the groups of patients within pulmonary hypertension. Do you recall that?

A. Yes.

Q. Which group do PH-ILD patients fall into?

A. That would be Group 3.

Q. You also mentioned precapillary PH. Which groups out of the five are precapillary, in your opinion?

A. Group 1, Group 1, Group 3, Group 4, and Group 5.

Q. And with respect to these groups, do you view them as strict delineations, or do you have patients that may have a mix of different groups in your practice and experience?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Most commonly it is a mix.

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BY ATTORNEY DAVIES:

Q. Can you explain that? What do you mean by "Most commonly it is a mix"? What does that mean?

A. The patients we see don't behave in strict categories and frequently have comorbidities where they have some lung disease and pulmonary hypertension. Some heart disease and pulmonary hypertension overlaid with chronic thromboembolic pulmonary hypertension.

I said half jokingly that my favorite group of pulmonary hypertension is group 10 where you have some one, some two, some three, and some four, because some patients are never quite that keen.

These categories are man-made, and we kind of box ourselves into a corner by trying to put patients in distinct categories, and the patients don't always behave the way we would like it to be, so they tend to cross over.

Q. So it would be common to see a crossover, for example, of a patient who shows signs of PAH, Group 1 might also shows signs of Group 3 PH-ILD. Is that fair?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That's a common debate when it's a Group 1 with a little bit of lung disease and when it's a Group 3.
BY ATTORNEY DAVIES:
Q. So you would agree that in your practice you do see patients who are a mix of both Group 1 and Group 3; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It's very difficult to sort out well, you know, this percentage from Group 1 and this percent is from Group 3.
The question becomes how much lung disease is permissible in order to call it Group 1 versus Group 3. And it's a spectrum. And some people can look at the same case and say, Well, I think this is more Group 1, and other people might look at the same case and say, No, I think this is more Group 3.
When we look and try to make that delineation, we look at how severe the human dynamic impairment is, how severe the lung impairment is based on lung

function tests, and we look at the CAT scan to see how much lung scarring there is in terms of making that determination.
BY ATTORNEY DAVIES:
Q. In your experience, what percent of -- strike that.
So in your clinical experience, what percent of the PH patients with treatment you've overseen or been involved in have been a mix of more than one of the groups of PH?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's a hard number through the years to come up with. You know, I would say maybe one-third could have a compound into something else going on, but that's not something I actively collect to show.
BY ATTORNEY DAVIES:
Q. We've talked a lot about interstitial lung disease. What is interstitial lung disease, in your words?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The interstitium of the lung refers to the lattice lock network within the lung parenchymal which

surrounds the alveola or intersects. The interstitium of the lungs.
When there's infiltration of the interstitium usually in a diffuse matter by scarring or fibrosis and/or inflammation, the results are manifested in interstitial lung disease.
BY ATTORNEY DAVIES:
Q. And have there been other words that are used to describe interstitial lung disease in the literature?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The wording can be confusing.
BY ATTORNEY DAVIES:
Q. I agree.
A. Pulmonary fibrosis, it refers to lung scarring, and most of the patients with interstitial lung disease of note, especially those who have superimposed pulmonary hypertension, will have pulmonary fibrosis.
And then even within the endopulmonary fibrosis, if you open any textbooks, there are probably over 200 courses of pulmonary fibrosis. And so, one of the jobs we have when you see a

patient with ILD is to try to figure out what kind of ILD they have.
Q. When did you first begin treating pulmonary hypertension patients?
A. I remember seeing my first patient with primary pulmonary hypertension, which is what I used to call it when I was a resident in New York in the late eighties.
Q. What is primary pulmonary hypertension?
A. We changed the nomenclature. It's now idiopathic pulmonary arterial hypertension. It was changed in about 1996, if I recall. When I was a fellow at Cedar Sinai Medical Center, we were one of the few centers in the country to do the study of REE treprostinil.
So as a person who enrolled in the study as a fellow in 1988, and so you can say the late eighties was the first time I started treating. Although at that time we didn't know if the medication worked or not. But then REE treprostinil got approved in 1994, and then I was treating off of it.
Q. What was the first time you recall treating an ILD patient?

ATTORNEY DYKHUIS: Object to form.
Q. I'll rephrase it.
When was the first time you can recall treating a patient with ILD, interstitial lung disease?
A. I actually do remember the patient I had with ILD, idiopathic pulmonary fibrosis, and that was in 1982 when I was an intern back in South Africa. I didn't treat her, because we had no treatment. But that was the first time I saw a patient with interstitial lung diseases.
Q. Did that patient have -- also have pulmonary hypertension, or were they just -- not just, but did they solely have interstitial lung disease?
A. At that point, I don't think we were even aware of pulmonary hypertension complicating interstitial lung disease. We're talking 1982.
Q. Do you recall roughly when there was a recognition in the art of pulmonary hypertension complicating interstitial lung disease?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: If you go back to the literature, there are some papers from the 1980s describing pulmonary

hypertension complicating interstitial lung disease. It was only in the early 2000s that more literature began to emerge about this.
BY ATTORNEY DAVIES:
Q. You mentioned, I believe, a couple different kinds of PH-ILD. Is that correct?
A. I didn't.
Q. You didn't? Is there only one type of PH-ILD, in your mind?
A. Yeah. You have different kinds of ILDs. When you talk about PH-ILD as a group, and there's just one kind. It hasn't been segmented out. There might be some people who talk about severe pulmonary hypertension, and that came out from the European guidelines. But in my mind, it's all one big basket.
Q. With respect to the differences in the underlying ILD, in your opinion did the INCREASE study evaluate PH-ILD patients who had all the different kinds of underlying ILD, or were there some groups that were excluded?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We included many different forms of PH-ILD. Connective

tissue disease, the effect of interstitial pneumonias with IPF being the major subgroup. Chronic hypersensitivity being another one. CPFE, combined chronic fibrosis with emphysema being another one.
There are other courses, as I mentioned. Some of those are broad categories. I don't recall if we had occupational lung disease in there or not. If we did, it might have been one or two patients at the most.
BY ATTORNEY DAVIES:
Q. Any other types of ILD that were not covered by the patient population in the INCREASE study?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: What I would say is just numerically, probably 95 to 99 percent of the disease categories were covered by the INCREASE study.
So let me qualify that. I said in terms of causes, some of them are extremely rare. The most common ones and

what I'm trying to articulate is that of the universe of patients with interstitial lung disease, fibrotic interstitial lung disease, we probably covered the bases for 95 to 99 percent. And that's a rough guesstimate on my part.
BY ATTORNEY DAVIES:
Q. When was the first time that you recall prescribing treprostinil to a patient?
A. When it first became available subcutaneously, and I believe it was in 2002 or thereabouts.
Q. Do you recall what you used that to treat in 2022?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Some form of pulmonary arterial hypertension.
BY ATTORNEY DAVIES:
Q. And when is the first time you can recall using inhaled treprostinil in a patient?
A. I think it was approved around 2010, I believe. At least that's when the paper came out. So soon thereafter, I believe.
Q. When was the first time that you

used inhaled treprostinil to treat PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't recall that. What I would say -- and this goes back to that spectrum of Group 1 versus Group 3 -- there are patients who have lung disease whose hemodynamics are severe enough out of proportion, so to speak, from the lung disease that I would regard them as having Group 1 pulmonary arterial hypertension even in the context of having interstitial lung disease.
So under that guise, I would treat patients with PAH who had lung disease.
BY ATTORNEY DAVIES:
Q. When was the first time that you can recall treating a patient who had PAH with underlying interstitial lung disease with inhaled treprostinil?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I don't recall that.
BY ATTORNEY DAVIES:
Q. Was it before the INCREASE study?
ATTORNEY DYKHUIS: Objection to

form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. Okay. Was it soon after inhaled treprostinil's approval around 2009?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't think so. I doubt it. I don't recall specifically.
BY ATTORNEY DAVIES:
Q. Why did you choose to use inhaled treprostinil to treat patients with PAH and underlying ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We had the INCREASE study results, and I knew about them before the drug was approved.
BY ATTORNEY DAVIES:
Q. But you used inhaled treprostinil in PAH patients with underlying IDL before 2016, didn't you?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: You know, going back many years, I don't remember a distinct case, to be quite honest.

Just by virtue of the patient volumes I see with PH, with interstitial lung disease, I'm assuming that I probably did, but I don't know for sure. Any time distinctly that I remember using it was after the INCREASE study results were known and off-label at that time because the drug wasn't approved as yet.
BY ATTORNEY DAVIES:
Q. You were aware that others were using inhaled treprostinil to treat patients with PAH and underlying ILD before recruitment for the INCREASE study, though; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Based on some of the papers in the literature, it does appear so, yes.
BY ATTORNEY DAVIES:
Q. So why were you personally comfortable prescribing inhaled treprostinil to these PAH patients with underlying ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: As I said, any time I remember distinctly was after INCREASE

became available. Patients -- prior to that I would treat patients with some interstitial lung disease if their pulmonary hypertension was disproportionate and I regarded them as having more of a Group 1 phenotype.
Typically at that point inhaled treprostinil wasn't my go-to drug. The easiest drug to get was Sildenafil, which is generally what I used if I was going to treat patients who had any form of lung disease and associated pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. So even though you can't recall a particular time, you do agree that you used inhaled trepostinil to treat PH patients whose PH was disproportionate to their underlying ILD before the INCREASE study; right?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I probably did. We're going back many years now. If you look at one group of patients, and that's connective tissue disease patients like scleroderma who form at least about

30 percent of the Group 1 PH patients, if you look at the CAT scans, it's very unusual for them not to have some lung disease.

And so even if the clinical trials of Group 1 PH, there were likely a bunch of connective tissue disease patients who had some lung disease that we just didn't know about.

BY ATTORNEY DAVIES:

Q. So I believe you said even in the clinical trials of inhaled trepostinil for Group 1 PAH, there were likely some patients with underlying ILD as part of that study as well?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I'm speculating. What we -- for all the clinical trials in Group 1 PAH, what we used as the cut point to get into the study was the forced vital capacity.

If the forced vital capacity was greater than about 70 percent, then the patient goes into the study. Can we rule out that a patient with the FVC of 72 percent didn't have a little bit of

lung disease, no, we can't, but we don't know.

So I'm speculating that maybe there was some patients who were included in the study, but these were patients who were defined as Group 1 PAH based on our criteria at the time.

BY ATTORNEY DAVIES:

Q. I believe you said it was likely that such patients would have been in those studies; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: It's possible, and it's speculative on my part, because I don't know.

BY ATTORNEY DAVIES:

Q. When was the first time that you can recall treating a PH-ILD patient with inhaled trepostinil?

A. After the INCREASE study results came out. That's when I first can recall treating a patient with PH-ILD with inhaled treprostinil.

But it was a patient, once again, who had more of the Group 1 phenotype with more moderate to severe pulmonary hypertension.

Q. And when did the results come out for INCREASE?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I was first made aware of the results ruts, as I said earlier when you asked me earlier towards the end of February 2020. There was a press release from the company around that time just providing the top line results, and then there was a publication in the New England June Journal of Medicine which I think was around January of 2021.

BY ATTORNEY DAVIES:

Q. And when was the first time that you recall treating a PH-ILD patient with Sildenafil?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I don't recall exactly, you know, going back 15 years, maybe more.

BY ATTORNEY DAVIES:

Q. So at least 15 years ago?

A. It could have been less than that. I don't know.

Q. But it would have -- you would have

treated a patient, a PH-ILD patient with Sildenafil before receiving the results of the INCREASE study; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Let me qualify that. These are patients who had more of a PAH phenotype in the context of some underlying interstitial lung disease. So I wouldn't regard them as PH-ILD. I would regard them as having some lung disease but more of a Group 1 PAH phenotype.

BY ATTORNEY DAVIES:

Q. When was the first time under your definition of PH-ILD you can recall treating a patient with Sildenafil?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: PH-ILD, if you go by the new definition versus the old definition, MPAP, mean pulmonary artery pressure greater than 20, greater than 25. It's a spectrum. And only if they were on the more severe end of the spectrum would I treat them.

So when you say PH-ILD, it was

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around that time, but it was the much more severe patients who had more of the Group 1 PAH phenotype.
BY ATTORNEY DAVIES:
Q. You said it was around that time. What time are you referring to? About 15 years ago?
A. About 15 years ago.
Q. When is the first time that you recall using Iloprost to treat PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We were part of the a study that's called Active Study looking at Iloprost to treat pulmonary hypertension associated with IPF.
So it was a specific IPF subpopulation of ILD, and it was a negative study. And I don't recall ever using inhaled Iloprost for pulmonary hypertension with interstitial lung disease.
BY ATTORNEY DAVIES:
Q. You mentioned the phrase earlier that in some of these patients their pulmonary hypertension is out of proportion to their

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underlying ILD.
Do you recall saying that?
A. I do.
Q. And when you write prescriptions that would have been off-label at the time for PH-ILD patients, is that the language that you use on those prescriptions when you prescribe inhaled treprostinil?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: As I said, I don't recall prescribing it. I withdraw that. I thought you said, I heard inhaled Iloprost. Inhaled treprostinil.
The language I would use post-INCREASE was that this patient gets to have interstitial lung disease, but clearly the pulmonary hypertension is out of proportion to the extent of the underlying interstitial lung disease; therefore I believe they have a Group 1 phenotype.
BY ATTORNEY DAVIES:
Q. Did you use that language and descriptions for inhaled treprostinil prior to results of the INCREASE study?

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ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't recall doing that.
BY ATTORNEY DAVIES:
Q. You never recall doing that?
A. As I mentioned, my go-to medication at that time just because it was cheaper to get a hold of and easier was Sildenafil. Can I attest to that a hundred percent? I can't remember every prescription I wrote. But that wasn't my standard practice by far.
Q. So sitting here today, you have no recollection of ever prescribing inhaled treprostinil in a PH-ILD patient prior to receiving notice of the results of the INCREASE study; is that correct?
A. Not to my recollection, but once again, I can't remember every prescription I've written.
Q. And even though you don't have a specific recollection, you would agree that probably did happen prior to you receiving the results of the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't recall it

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happening.
BY ATTORNEY DAVIES:
Q. Okay. Do you believe it did happen nonetheless?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: I don't recall it happening.
BY ATTORNEY DAVIES:
Q. And I'm not asking whether or not you recall or not. I'm saying do you believe that it happened based on the number of patients that you saw, based on the lack of clear delineations between the groups of PH?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I don't think it happened, because I don't believe it happened, but I cannot attest to it a hundred percent, having written thousands of prescriptions over the years. I don't know.
BY ATTORNEY DAVIES:
Q. You mentioned -- you mentioned using Sildenafil for treatment of PH-ILD; correct?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: For patients who had some ILD and associated pulmonary hypertension that appeared more severe than the extent of the underlying lung disease. I do want to make that distinction rather than the broad blanket term of PH-ILD, which can be any PH in the context of ILD.
BY ATTORNEY DAVIES:
Q. And with regard to those patients, in your opinion their PH-ILD was treated; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Are you referring to the PH component or the ILD component?
BY ATTORNEY DAVIES:
Q. Well, let me -- is there a distinction in your mind?
A. Yeah, we treat the ILD and we'll treat the PH. PH-ILD is really two diseases together.
Q. So if I have a PH-ILD patient and I treat the PH component in that patient, do you consider that treatment of PH-ILD or not?
ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Are you talking about currently or prior to the INCREASE study?
BY ATTORNEY DAVIES:
Q. Let's start with prior to the INCREASE study.
A. Yes. I considered treating PH-ILD in that context, but once again, I feel like I have to qualify it every time you mention PH-ILD prior to the INCREASE study as patients who had pulmonary hypertension that appeared to be out of proportion to their interstitial lung disease.
Q. When you say prior to the INCREASE, you're talking about the prior to initiation of that study or some other time point?
A. Prior to the results coming out of the meeting where there were results.
Q. So prior to you being aware of the results from the INCREASE study, if you prescribed a medication to a patient with PH-ILD, did you consider -- let me start this whole thing over.
Prior to you hearing the results of the INCREASE study, did you consider yourself to have treated PH-ILD in a patient if you just impacted the PH component of the disease?

ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I didn't know if I was treating it. I was hoping I was treating it. I'd like to make the distinction of treating PH versus helping the patient, because we know that these drugs, Sildenafil, inhaled treprostinil, they lower the pressures in the lung. That's treating the pulmonary hypertension.
What I didn't know is if treating and lowering the pressures potentially would result or manifest as a clinical benefit.
BY ATTORNEY DAVIES:
Q. And what in your mind was a clinical benefit?
A. There could be multiple manifestations of the clinical benefit. If the patient comes back and says, Gosh, I feel better, that's benefit. If they come back and their six-minute walk distance has increased, they say I feel better, then that's a benefit.
So in my mind, every patient who I've

treated like that was an end of point study. They told me how they were doing. If they felt better, great. If not, then frequently I would stop the medication.
What I didn't know, even if they felt better, is whether or not it was an effect of the drug or not. Because you know that there could be a big placebo component even if you go to the INCREASE study. There were patients who were treated with inhaled trepostinil -- sorry, with placebo who had increases in their walk distance. The only way you can tell if the drug works or not are these big population-based studies like INCREASE, where you have a large group that gets drug and a large group that doesn't get drug.
Q. So in an individual patient setting, how do you know if the treatments that you are giving to your patients are actually effective or not since it's not in a large group setting?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: As long as a patient tells me they feel better, I don't really concern myself if it's a placebo effect or if it's real. If they feel better,

I'll do anything and continue any medication that they perceive as making them feel better.
BY ATTORNEY DAVIES:
Q. But in your mind, is treatment -- in your mind, is the definition of treatment only those instances where the drug has a demonstrated impact on the patient?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: No, that's not my definition of treatment.
BY ATTORNEY DAVIES:
Q. Okay. If there's a placebo treatment, is that treatment?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Yes. If the patient feels better, you've done something via placebo and it's resulted in improvement, so I would regard that as treatment.
BY ATTORNEY DAVIES:
Q. Treprostinil is in part a vasodilator; correct?
A. That's correct.

Q. What hemodynamics impacted by treprostinil, in your mind, inform whether or not there has been a treatment effect?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: If you go back to the definition, if you lower the mean pulmonary artery pressure and you lower the pulmonary vascular resistance, then the drug has acted as a vasodilator and has been a treatment effect.
The key element is whether or not that treatment effect translates to clinical benefit for the patient. Let me go back as an example to the RISE IP study where we know clearly that riociguat is a pretty potent vasodilator and lowers the pressures, and yet patients didn't benefit and in actual fact they were harmed by them riociquat.
So A frequent effect on the pulmonary hypertension doesn't equate necessarily to clinical benefit for the patient.
BY ATTORNEY DAVIES:
Q. Do you measure -- in your clinical

practice, do you measure the hemodynamics of patients on inhaled trepostinil as part of monitoring those patients?
A. Typically, no. Once we start them on treatment, unless an additional question arises, it is an invasive test on riociquat and I ask a specific question you need answered by the test, then typically no.
Q. Which hemodynamic -- strike that.
Which improvements in which hemodynamic parameters would, in your mind, be indicative of a clinical improvement?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: None.
BY ATTORNEY DAVIES:
Q. None?
A. None.
Q. Is it your testimony that based on hemodynamic data you cannot predict in any way the clinical effects of treprostinil?
ATTORNEY DYKHUIS: Form.
THE WITNESS: Let me differentiate Group 1 from Group 3.
BY ATTORNEY DAVIES:
Q. Okay.

A. Because Group 1, the hemodynamic effect is a good surrogate for likely clinical benefit. There probably have been instances, I can't cite them and I'm sure there have been instances of drugs that have had a hemodynamic effect that haven't come to market because they haven't manifested clinical benefit.
In Group 3 or PH-ILD, all bets are off, because now you have the superimposed interstitial lung disease, and so my definitive no was more directed to PH-ILD.
What I'm saying is Group 1 is a good surrogate, not always, but in Group 3 it's not necessarily a surrogate for benefit.
Q. Why, in your mind, is it not necessarily a surrogate for clinical benefit in Group 3?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Because you have the added layer of the pulmonary parenchymal interstitial lung disease. I'm happy to do a deep dive into it if you like. Let me do it so maybe you can -- because I'll try to do it as best I can.

BY ATTORNEY DAVIES:
Q. Go ahead.
A. If you have fibrosis of the lung, there are many things that contribute to the pulmonary hypertension. You have obliteration of the vessels, you have distortion of the vessels. There's a lot of different things going on in the lungs as opposed to Group 1 PAH where they typically have normal lung disease, let's say.
When -- let's say you have 50 percent of your pulmonary vasculature that's totally obliterated and unavailable for perfusion, then the right side of the heart has to put out the whole cardiac outputs into 50 percent of the vasculature.
So when you talk about the velocity of the blood flow, the sheer stretch involved, we don't know if that's harmful to the vasculature itself. And we don't know when you have distortion of the vasculature and you have these accelerated blood cells coming in how that impacts overall well-being of the patient.
Another concept to remember is take the same example where you have 50 percent of your blood flow -- say a hundred percent of your blood flow going to residual 50 percent of the vascular,

and let's say the velocity has to be processed fast to maintain your cardiac output.
Well, you also need gas exchange between the alveoli line and the blood flowing through it, and now you have fibrosis interlaced. Typically in a normal person when a red blood cell traverses the alveoli and the capillaries, it gets fully oxygenated one-third of the way through.
But now you have a situation of fibrosis and you have these accelerated red cell particles that are more accelerated because there's been vasodilation, an ability to fix gas exchange becomes impaired.
So that just one example -- two examples of how lung disease makes it very different in terms of lowering the pressures enabling more blood to go through, and there can be a negative downside to that.
Q. Why, in your opinion, see a treatment affect with inhaled treprostinil in PH-ILD patients in the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I think a difference, for example, we can apply riociquat to what I just said. A

difference with inhaled treprostinil is, number one, it's inhaled. So most of the drug is going to the best ventilated areas of the lung.
If the drug is going to the best ventilated areas of the lung and dilating the blood vessels in those best ventilated areas, then you get the blood redirected to the best ventilated areas.
That's would be just one example of how that might be different to the scenario you I gave you, which is more applicable, say, to a systemically administered agent. You also have more drug deposition within the area of the lung where you want it to go compared to a systemically administered drug where in the context of fibrotic lung disease you don't know where the drug is going.
So more local deposition and, you know -- but to your point, that's how I was skeptical that the INCREASE study would be positive. And -- but at the end of the day it was unequivocably positive with benefit in the primary secondary

biomarker. And so thankfully it works and, you know, it's available to help the patients.
BY ATTORNEY DAVIES:
Q. You talk about VQ mismatch a number of times in your declaration.
Do you recall that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. What is VQ mismatch?
A. I thought I explained it pretty well in my declaration. I'm not going to read it. I'm sure you've read it.
Q. If you can explain it.
A. It's easier for me just to read from my declaration.
Q. That's fine.
A. I'll explain. For gas exchange to take place, you need VQ matching. The air going into the lungs and into the alveola sac has to be accompanied by blood through the capillaries to interface with the air.
If you have areas of the lung where you have VQ mismatch, there are two extremes of that.

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You can have no air and blood flow; and we refer to it as shunt. The area is being shunted to the lungs without opportunity for gas exchange.

If you have areas of the lung, opposite end of the spectrum where you just have air flow, no blood flow because there's been fibrosis, the blood vessels has been destroyed, then we could talk about that as dead space ventilation. Air is going in and going out and not participating in gas exchange.

Between those two extremes of dead space ventilation and shunt physiology, we have a gradation in the spectrum once again and VQ mismatch with the amount of ventilation going in doesn't match up with the perfusion going by.

Q. So a concern with giving a, for example, systemic oral vasodilator, maybe you actually exacerbate that VQ mismatch by attempting to have blood go to areas of the alveoli that can't actively participate in oxygen exchange; correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That is a theory of concern.

BY ATTORNEY DAVIES:

Q. Okay. Do you believe that theory?

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ATTORNEY DYKHUIS: Object to form.

THE WITNESS: It's possible that it does happen. It's possible that it happens in different lung units in the same patient.

There have been studies around this, I believe, for many years ago that maybe a test of VQ mismatch being an issue. I can't recall that study. I'm speculating, there are probably studies out there that demonstrated that.

So it's a theory, and it's something we lean on sometimes when you can't find a good explanation for worsening oxygenation.

So, I think it probably does happen in some patients, yes.

BY ATTORNEY DAVIES:

Q. In your opinion, was the fact that riociquat was a systemic orally administered vasodilator, do you believe that that was a reason for why you had increased death in the study population and the reason why that study failed?

ATTORNEY DYKHUIS: Objection to form.

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THE WITNESS: We don't know, but it could have been a contributing factor, but we don't know.

BY ATTORNEY DAVIES:

Q. I think you said one of the advantages of an inhaled therapy is that it actually is preferentially directed to the healthy portions of the lung and you avoid some of the concerns associated with the VQ mismatch. Is that correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Theoretically possible. Not healthy, relatively healthier, and so -- but you've got the general principle correct.

BY ATTORNEY DAVIES:

Q. In your opinion, is that part of the reason why inhaled treprostinil showed a clinical benefit in the INCREASE study?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: It's possible it might have had a role, but we don't know.

BY ATTORNEY DAVIES:

Q. What is your opinion?

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ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: Why the study was positive?

BY ATTORNEY DAVIES:

Q. Correct.

A. I don't know. I actually when I'm giving talks I get asked this question all the time. What is the reason, what's the biologic reason, and I don't think anyone can say for sure what the biologic reason is.

But what I say is we can make sure they have a sound biologic reason of why a drug should work but doesn't, or would you have some questions about how it does work and not know exactly and yet it has clinical benefits -- benefit. I would much rather take the benefits to the patient than know exactly how it works.

There are all these theories that, you know, it goes to the best ventilated areas. Just enough drug and the enough dose to provide benefit, but we don't know for sure how or why it works.

You know, on a cellular level there are all sorts of pathways to show positive benefits, and we don't know which one might have been of benefit to

the patients. So we can't pinpoint exactly how it works, and it probably works by multiple different ways in terms of providing benefit.
Q. We talked earlier about the fact that Tyvaso was initially approved in Group 1 in 2009.
Do you recall that?
A. Yes.
Q. That was a nebulized formulation in 2009; is that correct?
A. Yes.
Q. So in 2009 with the approval of Tyvaso inhaled, practitioners in the field would have recognized that that treprostinil was going to be preferentially delivered to the vaso ventilated portions of the lung; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It was approved for Group 1 PAH patients who generally don't have lung disease, so you don't have this VQ imbalance in Group 1 patients as you do with patients with lung disease.
I just want to come back to the question that you asked previously. There might be people who say that

inhaled treprostinil works because it's a vasodilator, it's clear it's a vasodilator that you see in patients and that's why it worked.
But in patients with lung disease, we know it's not as simple as that we have other drugs like riociquat, which are also very good vasodilators and it failed. So I think to say well, it's a vasodilator, it's obvious that it worked. It's kind of naive without taking into account the prior literature.
BY ATTORNEY DAVIES:
Q. Isn't the difference in administration between riociguat being systemically administered -- let me start over.
The fact that riociguat is a systemic vasodilator because it's given orally, it's a differentiating factor as compared to inhaled treprostinil; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It's one of many differentiating factors.
BY ATTORNEY DAVIES:
Q. I want to go back to a question I

asked you earlier.
So after receiving -- after you received the first report of results from the INCREASE study, did you believe that you were treating the PH-ILD in a patient if you were just treating the, or impacting the PH component?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I want to make sure I understood that correctly. Whenever I treat a patient, I want to benefit the patient.
So after the INCREASE study, I believe that we were treating the patient because they were having benefit.
BY ATTORNEY DAVIES:
Q. So your -- is it true that your definition of treatment, both before and after the INCREASE study, was that if you saw a benefit in the patient, it didn't matter whether the effects of the inhaled treprostinil were on PH or were on the ILD component. Either way you consider that to be treatment if there was an improvement in the patient?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Improvement in the

patient is very likely -- much more likely related to the PH component.
When you treat the fibrosis component and you've seen this with anti-fibrotic drugs, all it does is delay progression of the fibrosis. Once scarring is there, you can't reverse it. So my belief was that it was related mostly to an impact on the pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. Okay. Do you believe that inhaled treprostinil in the INCREASE study had any role on reversing the pulmonary fibrosis in those patients?
A. That would be speculative. I mean, there are mechanisms whereby it could have anti-fibrotic properties, and that's the reason for the Teton study to see if we can validate that.
What we saw, specifically in the subgroups post hoc analysis or the numbers, is that it did appear, the FVC was about the zero line, the line of unity starting out at 16 weeks.
So it gives the appearance of apparent improvement. But the error bars crossed the zero line, and so there can be vacillations in the FVC.

So we don't know. To say that there's an improvement in the fibrosis is very speculative.
When you have fibrosis being laid down, there are various stages of fibrosis from early collagen deposition, fiberblast activation, early scarring to end stage honeycombing.
Is it conceivable that anti-fibrotic drugs can reverse the earlier stages of fiberblast proliferation and collagen deposition? It's quite possible.
But advanced fibrosis it doesn't reverse. Whether the inhaled treprostinil has any independent anti-fibrotic properties, we don't know. What we can say about the post hoc analysis from the INCREASE study was that it was hypothesis-generating and now we're testing that hypothesis in the Teton program.
Q. So based on that, is it fair to say that you believe the majority of the treatment effects that you saw an increase for inhaled trepostinil are due to treatment of the PH component?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I believe that's much more likely.

BY ATTORNEY DAVIES:
Q. Was the INCREASE study designed to evaluate the treatment effects of inhaled treprostinil on the fibrosis component of PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No, it wasn't.
BY ATTORNEY DAVIES:
Q. Why not?
A. Because at that time before the study we had no notional idea that it might have independent anti-fibrotic properties.
Q. And even after the INCREASE study, you can't say with certainty whether or not treprostinil has anti-fibrotic properties and that's why you're conducting additional studies; correct?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: That's correct. It's been shown in animal models that it might have anti-fibrotic properties. But whether or not that translates into human subjects remains to be determined by the Teton study.

BY ATTORNEY DAVIES:
Q. Prior to the INCREASE study, did you believe inhaled treprostinil would be safe in the PH-ILD patient population?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: We didn't know, and that's why spirometry, which captures FVC, was included as a safety endpoint.
BY ATTORNEY DAVIES:
Q. So was the INCREASE study designed to assess the impact of inhaled treprostinil on the PH component of PH-ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It was designed to evaluate if it had clinical benefit. It wasn't designed to test PH, because otherwise we would have had to write off that as our primary endpoint.
BY ATTORNEY DAVIES:
Q. Was the INCREASE study designed to evaluate the clinical benefit of inhaled treprostinil in the PH component of PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The thought was that

if it were to have benefit, it would be through the PH component, yes.
BY ATTORNEY DAVIES:
Q. Was it designed to actually assess that, though? Was it powered to assess that?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: The clinical benefit, yes.
BY ATTORNEY DAVIES:
Q. Sitting here today, what treatments that are approved for Group 1 PH have you prescribed in your Group 3 PH patients?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I have to go through them all in my head. I mentioned Sildenafil. Certainly not riociguat. Not inhaled iloprost. We don't use anti-receptive antagonists.
(Reporter clarification)
Q. Maybe just let me reask my question and we'll just try to go through a little bit slower.
So what treatments approved for Group 1

pulmonary hypertension have you prescribed for Group 3 patients?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Without going through the exhaustive list of available therapies, Sildenafil, as I mentioned. Inhaled treprostinil, IV treprostinil, and maybe subcutaneous treprostinil. And maybe tadalafil, t-a-d-a-l-a-f-i-l.
BY ATTORNEY DAVIES:
Q. With respect to IV treprostinil, did you give that to a Group 3 patient prior to receiving the results of the INCREASE study?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: IV and subcutaneous treprostinil are given parenchymally, which means subcutaneously or intravenously. Those we reserve for the most severe form of hypertension, so these were patients clearly below the Group 1 PAH component but had some lung disease in the context of that. Those are the patients who got those therapies.

BY ATTORNEY DAVIES:
Q. You prescribed that in those patients prior to receiving the results of the INCREASE study; correct?
A. Correct.
ATTORNEY DYKHUIS: Object to form.
Q. With Tadalafil, did you prescribe that in Group 3 patients prior to receiving the results of the INCREASE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Probably so. There's very little data on Tadalafil. And I might have mentioned it because I might have. As I mentioned, Sildenafil was more about go to PDE5 inhibitor. Tadalafil is just a more convenient version of a PDE5 inhibitor given once a day versus three times a day.
BY ATTORNEY DAVIES:
Q. In your opinion, are there any hemodynamic changes that would be indicative of an improvement in exercise capacity for a PH-ILD patient?
ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: None.
BY ATTORNEY DAVIES:
Q. In your opinion, do hemodynamic changes have any predictive benefit in suggesting an improvement in exercise capacity for a PH-ILD patient?
ATTORNEY DYKHUIS: Objection.
THE WITNESS: I apologize.
BY ATTORNEY DAVIES:
Q. That's no problem at all.
A. I just want to note that I apologized for the cough. I don't know if you capture a cough, but I was apologizing for the record. For the record, I'm coughing a lot, and I apologize for that.
Q. Not a problem. Would you like me to repeat the question?
A. Yes.
Q. So in your opinion, do hemodynamic changes have any predictive value in suggesting an improvement in exercise capacity for a PH-ILD patient?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: What I would say is that they do have somewhat of a

predictive capability in the more severe patients that I just described to you. The ones who are so severe that they require parenchymal therapy.
So when you have very high pressure in a high pulmonary vascular resistance there's a greater likelihood and certainly a greater hope that we will see some benefit.
Otherwise, for more general population of PH-ILD, most of whom have more mild to moderate pulmonary hypertension, they are generally unpredictive.
(Discussion held off the record.)
ATTORNEY DAVIES: We can keep going until lunch and we can take a break? It's another 30 minutes?
ATTORNEY DYKHUIS: Sure.
BY ATTORNEY DAVIES:
Q. And if you decide that was a bad decision and you want to break before then, you can let me know.
A. Yeah.

Q. Is six-minute walk distance a measure of increased exercise capacity?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: We regard it as a surrogate for what patients might be capable of doing. So the answer to that would be yes.
BY ATTORNEY DAVIES:
Q. Other than six-minute walk distance, are there any other measures of increased exercise capacity?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There are things like cardiopulmonary exercise testing. There are --
BY ATTORNEY DAVIES:
Q. I'm sorry, go ahead.
A. There are patient report outcomes where we ask them about how much they can do. The other test that we generally go to, like the Shekel test, and so there are various forms of evaluating exercise. But the six-minute walk is the most commonly accepted one in terms of what we do in the clinic and in clinical trials.

Q. Are you currently using inhaled treprostinil to treat PH-ILD patients?
A. Yes.
Q. Are you using nebulized Tyvaso to treat PH-ILD patients?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Nebulized and the dry powder inhaler.
BY ATTORNEY DAVIES:
Q. Have you seen any switching in your PH-ILD patients who you've started on the dry powder inhaler switching to the nebulized Tyvaso?
A. Yes.
Q. And why do you think that is occurring?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: They sometimes don't tolerate it. Sometimes because it's one breath, especially in the context of interstitial lung disease, they might not be able to take a deep breath to get the drug down into the areas you want it.
So in some patients I feel more comfortable using the nebulized version because I feel more assured that at least

they're taking six, nine, 12 risks that some of the drug is getting down versus one hit of the DPI, one cough, and the drug comes out.
So I think it's the most reliable way of treating these patients that I do use both, depending on the individual patient. But you can well imagine someone coughing right after they get the DPI and they get into drug.
BY ATTORNEY DAVIES:
Q. Do you have a sense for the percent of patients that you started on Tyvaso DPI that have switched back to the Tyvaso nebulized formulation?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: 25, 30 percent. I'm guessing, though, that it's not one of two.
BY ATTORNEY DAVIES:
Q. Are you familiar with the Dreamboat device?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I am not.

BY ATTORNEY DAVIES:
Q. Are you aware that the Dreamboat is the dry powder inhaler that's used for Tyvaso DPI?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm familiar with the DPI for Tyvaso. I didn't know if it was called the Dreamboat.
BY ATTORNEY DAVIES:
Q. In your opinion, is the DPI for Tyvaso a high-resistance device?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I believe it is a high-resistance device.
BY ATTORNEY DAVIES:
Q. What is a high-resistance device?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I've never researched it myself, to be honest, but I suspect when they take a breath in, it's more of a resistance to taking the breath in versus a low-resistance device.
BY ATTORNEY DAVIES:
Q. Why do you believe that the Tyvaso DPI device is a high-resistance device?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I have no idea.
BY ATTORNEY DAVIES:
Q. Okay. What, in your opinion, is a pulsed inhalation device?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: One that's not continuous, that it comes out in one pulse.
BY ATTORNEY DAVIES:
Q. Is the Tyvaso DPI a pulse inhalation device?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I believe it is regarded as such.
BY ATTORNEY DAVIES:
Q. And what is that belief based on?
A. That you actuate it, and it comes out as a pulse while the patient is taking a breath in.
Q. When you say you actuate it, you're equating the breath in with the pulse; is that correct?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm assuming it is.
BY ATTORNEY DAVIES:
Q. But you don't know for certain; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I think it's a good assumption.
BY ATTORNEY DAVIES:
Q. Okay. But you don't know for certain; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I don't know the technicalities of when the pulse comes out versus when the patient takes the breath in. I've never taken a hit myself. I might have, you know, on a placebo device when it first came out, but I don't know technically how the pulse relates to the breath going in.
BY ATTORNEY DAVIES:
Q. Have you ever -- sitting here today, do you recall any publication where you referred to a dry powder inhaler as a pulse inhalation device?
ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I've written many things over the years, and it could be something where there's something about a pulse inhalation device, but I don't recall if I did or I didn't.
BY ATTORNEY DAVIES:
Q. And sitting here today, you can't recall any presentation that you've given where you've referred to a dry powder inhaler as a pulsed inhalation device; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I've given many presentations. And I don't know if I have or I haven't. I may have.
BY ATTORNEY DAVIES:
Q. Sitting here today you can't recall any particular circumstance; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.
Q. Do you know whether the Tyvaso DPI pulses the drug independently of the patient's inhalation?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No, the patient has got to be taking a breath in for the

pulse to occur. Otherwise, you know, they would be walking around with it in their pocket and it would go off. So there's got to be something to activate the device.
BY ATTORNEY DAVIES:
Q. Do you consider the nebulizer that's provided with Tyvaso to be a pulsed inhalation device?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: My understanding is that it's more continuous. That's my understanding.
BY ATTORNEY DAVIES:
Q. What is that understanding based on?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The fact that it's a nebulizer, which are generally continuous. Whether there are little pulses in the context of that nebulizer, I don't know, but I've always regarded nebulizers to be more continuous.
BY ATTORNEY DAVIES:
Q. And you have never seen the dry powder inhaler for Yutrepia; correct?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Not that I can recall.
BY ATTORNEY DAVIES:
Q. You've never seen any schematics or drawings of the dry powder inhaler for Yutrepia; correct?
A. I believe I might have.
Q. Okay. When do you believe you might have?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There might be a picture in my declaration. I thought there was something from the proposed label. Let's see if I'm correct. I thought there was. I could be wrong. No.
I thought there might be a little picture of it on this label, but there isn't. My apologies.
I might have -- you know, it's been around for all these years, I can't answer to if I haven't Googled an image before, so I probably have, but I'm not a hundred percent certain.

BY ATTORNEY DAVIES:
Q. Okay. Sitting here today, you have no knowledge of whether the Yutrepia DPI provides the powder continuously or in pulses in any way; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: My assumption is if it's a dry powder, then it should be pulsed, that's my assumption.
BY ATTORNEY DAVIES:
Q. But you can't say with certainty because you've never seen the device or seen it described; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.
BY ATTORNEY DAVIES:
Q. You mentioned that the Tyvaso DPI, in your opinion, was a high-resistance device. Do you believe that you would see less switching if patients were provided with a low-resistance DPI with the same efficacy?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: No idea. I don't think it's necessarily a function of the

resistance.
BY ATTORNEY DAVIES:
Q. What do you think it's a function of?
ATTORNEY DYKHUIS: Form.
THE WITNESS: Just general tolerability. Every patient is different, and there could be an irritation of the particles.
I would hypothesize if you have a low-resistance device and suddenly you get a rush of the particles to the back of your throat, that might induce more coughing and perhaps make patients less tolerable of the device.
BY ATTORNEY DAVIES:
Q. In your clinical practice, how do you determine whether there's been an improvement in exercise capacity in your patients?
ATTORNEY DYKHUIS: Objection to form.
Q. Let me restate that.
In your PH patients, how do you determine whether there has been an improvement in exercise-type capacity?

ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Talking to the patients always helps in terms of what they can do versus what they used to be able to do. And then we look at the six-minute walk test, and that gives us an idea of what the exercise capabilities are.
BY ATTORNEY DAVIES:
Q. What information would a patient provide you, short of performing a six-minute walk test, that would inform you as to improvement of the exercise capacity?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: They might come in and say, Gosh, Doc, thanks for that medicine. I feel so much better. Before I got shortness of breath going to the bathroom, and now I can go to the bathroom and get the mail that I couldn't do before. That's really dependent on the individual patient.
BY ATTORNEY DAVIES:
Q. What is an exacerbation of

interstitial lung disease?
A. I believe you asked that earlier, but just to reiterate, our form of the definition from our society where it's a worsening of shortness of breath over approximately a four-week period accompanied by worsening oxygenation, accompanied by increased infiltrates on chest imaging, and ruling out other potential causes for this such as heart failure, for example.
Q. And how would you determine whether there had been a reduction in one of those exacerbations?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: You cannot determine that on an individual patient basis. It takes large studies, much like we had in INCREASE where you compare the one group to the other to see what the incidence is in the one group versus the other.
So on an individual patient you can't know if you're having any impact on preventing acute exacerbations.
BY ATTORNEY DAVIES:
Q. So in a patient you couldn't determine whether or not you were improving an

exacerbation. You would need to look at a large study population to do that; correct?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: What you just said is a little bit different. Prevention versus treatment, which is what you just alluded to, I think.
Treatment of acute exacerbations is very, very difficult. What we saw in the INCREASE study was fewer acute exacerbations. So less incidence of acute exacerbations versus as a treatment for acute exacerbation.
BY ATTORNEY DAVIES:
Q. We talk about FVC. Could you tell me what FVC stands for?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Forced vital capacity.
BY ATTORNEY DAVIES:
Q. What is forced vital capacity?
A. It's the amount of air that a patient can blow out after taking a full inspiration and then blowing out as hard as they

can until they can't blow out anymore. That would be the forced vital capacity.
Q. And how would you determine in a patient that there has been an improvement in forced vital capacity?
A. There's some inherent variability around the forced vital capacity as much as 10 percent. So if there's a 3 percent improvement, we don't know if it's test-test variability or if it's real.
When we get beyond the 10 percent number, either up or down, then you can be more certain that the change you're seeing is real.
Q. So if you're seeing less than a 10 percent change in forced vital capacity in a patient, you personally would not be confident that that's a real change; correct?
ATTORNEY DYKHUIS: Objection.
THE WITNESS: Like everything else, it's a spectrum. Nine percent is more of a change than 1 percent, so there's no definite cutoff. And 11 percent is worse than 10 percent, but we typically regard 10 percent as a threshold of a meaningful change. But it

could be that changes of less than 5 percent are meaningful, but because it's a spectrum it's not as meaningful as a 10 percent change.
BY ATTORNEY DAVIES:
Q. In the INCREASE study, do you recall to the extent there was a change in FVC if that was greater than or less than 3 percent?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Are you talking about the difference to the placebo arm?
BY ATTORNEY DAVIES:
Q. Correct.
A. I don't recall what that exact number was. I do recall that it was statistically significant. The 5 percent, 10 percent quality is for the individual patient. For a population-based study where you have many contributors, you can have a change as small as 1 or 2 percent which might be statistically significant.
Q. But you could not determine whether there had been a -- let me restart here.
You couldn't determine in a patient whether there had been a statistically significant

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difference in FVC; correct?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: No. As I mentioned previously, you can't determine statistically -- statistical significance in an individual patient.
ATTORNEY DAVIES: I'm going to move to some other stuff. Do you want to take a break for lunch now, because I think we have to grab something.
ATTORNEY DYKHUIS: Sounds good.
THE VIDEOGRAPHER: We are off the record at 11:51.
(Recess taken from 11:51 a.m to 12:46 p.m.)
THE VIDEOGRAPHER: We are on the record at 12:46.
BY ATTORNEY DAVIES:
Q. Welcome back, Doctor. I'm just going to grab two documents here.
So I'm marking as Exhibit Number 3 a publication entitled "Controlled Trial of Sildenafil and Advanced Idiopathic Pulmonary Fibrosis" by Zisman, et al., and bearing production

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number UTC_PH-ILD_010830 to -838.
(Exhibit 19 was marked for identification.)
Q. And, Doctor, I'm going to ask for your help in passing a copy to counsel as well.
A. (Witness complies with request.)
Q. My first question for you is have you seen Exhibit 3 before?
A. Yes, I have.
Q. And what is Exhibit 3?
A. It's a report of a controlled trial of "Sildenafil and Advanced Idiopathic Pulmonary Fibrosis" published in the New England Journal of Medicine in 2010.
Q. If you turn to page 627 of this paper, and it's near the bottom of the page the author says, "Although the study did not meet its prespecified primary outcome and the therapeutic efficacy of Sildenafil is far from established, our data provides the clinical equipoise needed to conduct further trials involving patients with advanced idiopathic pulmonary fibrosis."
Do you see that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm sorry. Where

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about did you say it was?
BY ATTORNEY DAVIES:
Q. If you go to the bottom of the first column --
A. Okay.
Q. -- do you see there's a sentence that says, "Although this study"?
A. Yes.
Q. And then if you continue on to the next column, it refers to the data providing the clinical equipoise regarding the trials. What is clinical equipoise?
A. Equipoise to me always means the balance, clinical balance, so they're suggesting that there should be further trials involving patients with advanced IPF.
Q. And does this study examine the impact of Sildenafil in six-minute walk distance in patients with advanced idiopathic pulmonary fibrosis?
ATTORNEY DYKHUIS: Object to form and foundation.
THE WITNESS: Yes, it did.
BY ATTORNEY DAVIES:
Q. Is this study referred to as the

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STEP-IPF study in your report?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes.
Q. I'm now going to enter as Nathan Exhibit 4 an article entitled "Sildenafil Preserves Exercise Capacity in Patients with Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction" published in Chest by Han et al. in June of 2013.
(Exhibit 4 was marked for identification.)
Q. Doctor, have you seen this paper before?
A. Yes, I have.
Q. What is this?
A. This paper, as best I recall, was a subgroup analysis of the STEP-IPF study in those patients who had echocardiographic evidence of right ventricular dysfunction.
Q. So in the Chest publication, are they describing an evaluation of a subgroup of the patients within the STEP-IPF trial that was described in Exhibit 3?
ATTORNEY DYKHUIS: Object to the form and foundation.

THE WITNESS: I'd have to check, but I don't think they talked about the STEP study, which is a post hoc study in the paper that was published in the New England Journal, and I think that I mentioned that, and I would need to read the paper to be certain about that.
BY ATTORNEY DAVIES:
Q. But you agree that Exhibit 2 is a subgroup study of the earlier STEP-IPF Zisman publication; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I do.
BY ATTORNEY DAVIES:
Q. And with respect to this subgroup analysis, I'm looking on the first page of Exhibit 62, in the -- under Results, do you see the Results section in that box?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I do.
BY ATTORNEY DAVIES:
Q. So at least with this subgroup of subjects, the authors report, "In the subgroup of subjects with RVSD, subjects treated with Sildenafil experienced less detriment in six-minute

walk distance, 99.3 meters, P equals .01 and greater improvement in SGRQ and EuroQol analog scores than subjects receiving placebo."
Do you see that?
A. I do.
ATTORNEY DYKHUIS: Object to form.
Q. Okay. I apologize. Just so it's -- and I screwed up the exhibit number, so just to make it clear, I apologize. I was referring to Exhibit 4 instead of Exhibit 62.
So in Exhibit 4 you would agree that the authors with respect to this subgroup are reporting a significantly -- a statistically significant improvement in six-minute walk distance with treatment of Sildenafil as compared to placebo; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's what they're reporting on, yes.
BY ATTORNEY DAVIES:
Q. They also report a significantly -- a statistically significant improvement in SGRC within this subgroup as well; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: SGRQ, yes.

BY ATTORNEY DAVIES:
Q. And they also report a statistically significant improvement in the EuroQOL visual analog scores within this subgroup of patients from the larger STEP-IPF study; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. So at least with respect to the subgroup of patients that are further analyzed in the Chest publication in Exhibit 4, the STEP-IPF trial showed safety and efficacy; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I disagree with that.
BY ATTORNEY DAVIES:
Q. Why.
A. Let me draw your attention to the primary publication, and in terms of the methods, if you go to the methods, if you go to page 621, the last paragraph.
"The trial was conducted in two periods: Period 1 was a 12-week double-blind placebo-controlled study of Sildenafil. Period 2 was a 12-week open-label extension with all

patients on Sildenafil."
Now, draw your attention to Table 3.
Q. I'm sorry, Doctor. Which are we --
A. Still the primary publication.
Q. Okay.
A. Table 3, this was an intent to treat analysis of mortality. So patients were analyzed in whichever group they were originally assigned to.
So if you look numerically, they were at week 28. There were four deaths in the Sildenafil arm, 11 deaths in the placebo arm. So it looks like numerically Sildenafil does better than placebo because this is an intent to treat.
Sometimes I say intent to treat is intent to trick. I'll show you the trick here. The trick is that all patients on placebo were switched to Sildenafil. So the additional deaths in the placebo arm were on Sildenafil. There were seven additional deaths. So safety, no.
When you do a post hoc analysis, you are taking out patients who died or dropped out, and at best I would say that Chest paper is hypothesis generating. But these numbers if they had analyzed the patients on therapy, the number of deaths would

have switched. There would have been 11 on Sildenafil and four on placebo, and that's why I disagree.

Sometimes you have studies that have discordant outcomes. They might make patients feel better, but patients can die earlier.

Q. The New England Journal of Medicine paper at Exhibit 3 looks like it was published in 2010; correct?

A. Correct.

Q. And you mentioned that you used Sildenafil in the treatment of PH-ILD patients; correct?

A. Correct.

Q. And did you continue to do so after the publication of this study in 2010?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I did if they had PH of sufficient severity. Another point around this is we don't know which of these patients have pulmonary hypertension because they didn't have riociquat. This was a study in advanced IPF, not in patients with PH and IPF.

BY ATTORNEY DAVIES:

Q. Going back to Exhibit 4, which is the Chest paper. You would agree though, that with respect to the subgroup reported on, in Exhibit 4, these patients did appear to have a significant increase in their six-minute walk distance of nearly 100 meters; correct?

ATTORNEY DYKHUIS: Object to the form.

THE WITNESS: After the patients who died dropped out and weren't analyzed and you take a specific subgroup, that's what's reported in the paper.

BY ATTORNEY DAVIES:

Q. Have you ever heard of the term "patient phenotyping"?

A. Yes.

Q. What's patient phenotyping?

A. That's looking at the chemical characteristics of patients that bind them together in terms of having specific clinical characteristics that warrant them being considered as a separate group.

Q. And what role does patient phenotyping play in -- let me ask you this. Did

patient phenotyping play any role in the design of the INCREASE trial?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I wouldn't characterize it as patient phenotyping. Patients had to have pulmonary hypertension associated with interstitial lung disease. If you want to call patients who are associated with pulmonary hypertension in a patient with interstitial lung disease phenotyping, then you can make that argument.

Let me follow that up as well by saying that STEP-IPF in the subgroup analysis grew to be short-term. The one study that you brought to my attention earlier, which was Sildenafil plus pirfenidone, which was a long term study, showed no difference between the groups.

So the longer term even if you infer that there was some kind of benefit from this, another robust randomized control study did not validate that these effects were -- you know, there were any long-term benefits.

BY ATTORNEY DAVIES:

Q. Do you know whether the patients that you've treated with -- strike that.

Do you know whether the PH-ILD patients you've treated show an improvement in six-minute walk distance?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Some of them do and some of them don't.

ATTORNEY DAVIES: I've marked as Exhibit 5 a publication titled "riociguat for Idiopathic Interstitial Pneumonia-Associated Pulmonary Hypertension, (RISE-IIP): A randomized Placebo-Controlled Phase 2B Study."

(Exhibit 5 was marked for identification.)

ATTORNEY DAVIES: I'm sorry, just for clarity of the record, it bears Bates numbers UTC_PH-ILD_010530 to -540.

BY ATTORNEY DAVIES:

Q. And, Doctor, what is this publication?

A. This is a report on the randomized controlled study of riociguat for idiopathic

interstitial pneumonia associated with pulmonary hypertension, which was a randomized double-blind controlled, placebo-controlled study.

Q. And this is the RISE IIP study that you've described earlier today?

A. That's correct.

Q. And this is the RISE IIP study that's talked about in your declaration?

A. Correct.

Q. And there's a Steven D. Nathan that's the first author on this publication. Is that you?

A. That would be me.

Q. You've testified that you believe that the study was a failure. Is that correct?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I wouldn't characterize it as a failure. It was successfully completed. The drug didn't work and appeared to be harmful to patients, but study itself was a very well-done study.

BY ATTORNEY DAVIES:

Q. At the time -- why was the trial stopped?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: The trial was stopped -- every study such as this randomized control study has a dataset for the monitoring committee. You look at the data, blind it and, you know, sometimes blind and sometimes not, making sure that there's no harm, no foul to the individuals that have entered and continue to be enrolled in the study. And that's a safeguard for patient safety.

And that effect, the monitoring committee meets every couple of months, looks at the data and decided when they looked at the data at one point that there was a signal of harm in the riociguat arm that warranted discontinuation of the study.

BY ATTORNEY DAVIES:

Q. Why, in your opinion, did you see the safety signals that required the study to be stopped?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: If you go Table 2 --

BY ATTORNEY DAVIES:

Q. Which page is that on, Doctor?

A. -785.

Q. Yes.

A. And you look at the main phase of the study and you see in the last horizontal deaths, you can see that in the main phase of the study there were eight deaths on riociguat and three on placebo, which numerically by itself is not a big difference. And any time a death happens, a monitoring committee recommends halting a study, they wouldn't be fairly certain of what's going on.

But then what happened is after the main phase, all patients were placed on long-term open-label extension.

Now go across to Column C and 4, and we see one death in the real arm and eight deaths in the former placebo arm. In other words, patients who are dying who were previously on placebo and then rolling over to receive open-label riociguat.

And there were more patients coming through the study who are going over from placebo to get riociguat. So the dataset monitoring committee did the right thing in informing us and getting us to

hold the study.

This goes actually back to the STEP-IPF study, because this was on treatment mortality. If STEP had done on treatment mortality those numbers, as I mentioned, would have flipped around and might have looked similar to this.

Q. Okay. Do you believe you saw the safety issues because of the -- you had the wrong patient population in the study?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That might have been a part of it.

BY ATTORNEY DAVIES:

Q. Riociguat was given to these patients orally; is that correct?

A. That's correct.

Q. So it would have had systemic effects?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: That's correct.

BY ATTORNEY DAVIES:

Q. If you go to page 781 and you see a little shaded box here in your paper that says, "Research in context."

A. Yes.

Q. Do you see there's a reference, it's about half the way down, to a small phase 2 randomized control study of riociguat suggested a beneficial response.
Do you see that?
A. Yes.
Q. It's about halfway down in the first column.
A. I see small phase two, yes, I see that.
Q. What study are you referring to there?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It was a study that had as the first author Marius Hoeper, H-o-3-p-e-r. I want to say it was published in the European Respiratory Journal, but I'm not a hundred percent certain about that.
BY ATTORNEY DAVIES:
Q. And why did you choose to discuss that publication in your paper on riociguat?
A. I want to provide a context for why riociguat was studied in this study, and that's phase 2 -- I would revise the phase 2A study,

provided scientific rationale for why it did not work in the study that we did.
And this is an example of Rio can -- will treat pulmonary hypertension or lower the pressures, but it was harmful to patients. So you have to divorce treating pulmonary hypertension away or from clinical benefit.
Q. In your declaration, you talk about when you presented the results of this RISE-IIP study you were, quote, admonished by one of the session heads.
Do you remember saying that?
A. I do.
Q. Other than being admonished by that one session head, did anyone else at the meeting admonish you for conducting this study with riociguat?
A. I don't recall that. As I said, I found the people in the audience, none of the other chairs jumped to my defense. You know, you could construe silence as complicity.
I do remember that Mario Succa [phon.] himself was sitting in the front row, and he tried to defend, you know, having done the study because he was the first author on the study that laid the

foundation for the study.
But, yeah, I don't know what other people are feeling, but the chairperson who was the chairperson in that session who was renowned leader in the PH field, and he might have influenced people in the field to believe what he espoused, and that was that we shouldn't be treating PH associated with lung disease.
Q. And in your report at Paragraph 84 you state that the session lead told you, "Everyone knows that treating pulmonary hypertension associated with lung disease does not work."
Do you see that?
A. I remember that, yes.
Q. And other than this one session chair, no one else at this meeting of over 500 participants expressed that view to you; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There was a lot of discussion afterwards and people coming up to me. I suspect that people were of that belief, and he had said what he said. There was probably no further need to come up and admonish me. The work had been done.

BY ATTORNEY DAVIES:
Q. Did anyone else at the meeting come up and admonish you for the work?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No one else came up to me, but I do believe that this thought leader, highly regarded in the PH field, probably reflects the views of many other people he was speaking for. It might not have just been speaking for himself. He might have been speaking for many other people, and he probably influenced a bunch of the people in the audience who ended up being the same after the session.
You have a negative study that harmed patients, and then the session lead, who is a very renowned figure in the PH world, admonishing me for thinking that treating PH and ILD could never work, and this should never have been done.
BY ATTORNEY DAVIES:
Q. Who was the session lead who admonished you?

A. Dr. Lewis Rubin.
Q. You had mentioned that this earlier -- this earlier paper by Hoeper laid the foundation for your RISE study; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.
BY ATTORNEY DAVIES:
Q. Okay. And in what way did that study lay the foundation for your RISE study?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It showed that Rio could potentially be a treatment modality for patients with pulmonary hypertension associated with interstitial lung disease.
BY ATTORNEY DAVIES:
Q. After your RISE study, do you personally still believe that in the way patient population Rio could be used for treatment of PH-ILD?
A. I can't rule it out. But I wouldn't start it in any patient. There could be one in 10 patients, but I don't want to knock off another three patients to find that one in 10 patient.
Q. When you say "one in 10 patients,"

what one in 10 patients do you believe it would be likely to work in for PH-ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I'm hypothesizing and speculating. I'm giving an example. Any medication that's harmful, it might be the odd patient that it's helpful, but we suspended it because we would harm more patients than helping. And those are the medications that are generally population-based regarded as harmful even though there might be one or two patients who actually benefit.
BY ATTORNEY DAVIES:
Q. Can you go back to Exhibit 3, which should be the Zisman, et al, paper.
A. Yes.
Q. And do you agree that this STEP-IPF study described in this publication showed the proof of concept for using a Group 1 therapy Group 3 PH?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: You can take proof of concept -- let me say that you could

pick out some of the results from the study like some of the secondary endpoints and say, Yeah, it benefited there, and maybe this is a therapy that you can consider, but it didn't prove anything. It was hypothesis-generating.
Let me qualify that. The Hoeper article was proof of concept as well, and then subsequently we had a follow-up study that went the other way and proved to be harmful.
So proof of concept don't always equate to a positive study and can result in a negative study.
BY ATTORNEY DAVIES:
Q. So when you used the term "proof of concept" with respect to a clinical study, what do you intend that to mean?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: As proof that the concepts of what you're trying to treat with what you're trying to treat must be a beneficial therapy. It's the concept that subsequently remains to be further tested.

BY ATTORNEY DAVIES:
Q. And when -- what would be required in your mind to show that a proof of concept study actually results in treatment? Does that require a phase 3 placebo-controlled randomized trial?
A. Correct.
ATTORNEY DYKHUIS: Object to form, foundation.
Q. I'm going to pass you two documents, Doctor. The first is Exhibit 6, titled "Nintedanib."
(Exhibit 6 was marked for identification.)
A. Okay.
Q. It's titled "Nintedanib."
A. Correct.
Q. Plus Sildenafil inpatients with idiopathic pulmonary fibrosis. The first author is Martin Kolb published in the New England Journal of Medicine 2018, bearing Bates numbers beginning UTC_PH-ILD 010487.
And I'm also going to pass you Exhibit 7, which is Supplementary Appendix and refers to the New England Journal that I just identified as Exhibit 6. I'm going to pass you that.

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(Exhibit 7 was marked for identification.)
ATTORNEY DYKHUIS: Wait. Exhibit 6?
ATTORNEY DAVIES: Exhibit 6 is the New England Journal of Medicine article, and then Exhibit 7 is the supplementary appendix to that same article.
ATTORNEY DYKHUIS: Thank you.
ATTORNEY DAVIES: Okay.
BY ATTORNEY DAVIES:
Q. So have you seen Exhibit 6 before, Doctor?
A. Yes, I have.
Q. And does Exhibit 6 describe the end-stage study that's discussed in your declaration?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, it does.
BY ATTORNEY DAVIES:
Q. And if you look at Exhibit 7, is Exhibit 7 the Supplementary Appendix that the authors provided along with the publication of their article in the New England Journal of Medicine in Exhibit 6?

ATTORNEY DYKHUIS: Object to form and foundation.
THE WITNESS: Yes, it is.
BY ATTORNEY DAVIES:
Q. What were the authors -- what drug was being examined in the end-stage study that's described in Exhibit 6?
A. Sildenafil.
Q. In what patient population was it being examined in?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Patients with idiopathic pulmonary fibrosis who are on Nintedanib.
BY ATTORNEY DAVIES:
Q. Would that include PH-ILD patients?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It might. It doesn't look for PH. But there might have been some patients in there who had PH.
BY ATTORNEY DAVIES:
Q. What was the measure that they used for the primary outcome in the end-stage study described in Exhibit 6?

ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The primary endpoint was changed from baseline in the total score in St. George's Respiratory Questionnaire at week 12.
BY ATTORNEY DAVIES:
Q. And did that show an improvement? Did they see an improvement in the use of that questionnaire after treatment with Sildenafil or not?
A. No, they did not.
Q. Okay. Can you turn to Exhibit 7.
A. I've got it.
Q. Can you turn to Figure S3.
A. (Witness complies with request.) Yes.
Q. What is described in Figure S3 of the Exhibit 7 supplementary appendix?
ATTORNEY DYKHUIS: Objection to form and foundation.
THE WITNESS: This is a figure depicting the two arms of the study looking at change from baseline in the UCSD shortness of breath questionnaire at the time from zero to 24 weeks.

BY ATTORNEY DAVIES:
Q. So if the authors had used the UCSD shortness of breath questionnaire, do you agree that their treatment with Sildenafil would have shown an improvement over placebo?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That is, I would say, speculative.
BY ATTORNEY DAVIES:
Q. Why do you say it's speculative?
A. Once you choose your primary endpoint, you are a prisoner of your primary endpoint. If you have 20 secondary endpoints in a clinical study, invariably one of them is going to be positive and you can go back and say, If we had chosen this as our primary, this would have been a positive study. This is, once again, baseline-generated.
Q. They use the same data in Figure S3, though, that they use for their analysis using the St. George's respiratory questionnaire; correct?
ATTORNEY DYKHUIS: Object to form. Excuse me.
THE WITNESS: You have to direct me to that figure so I can compare them

off the primary. Actually, it's right next to it. It's Figure S2.
BY ATTORNEY DAVIES:
Q. Right.
A. So you're asking me the same analysis in Figure S3 is the same as S2?
Q. Correct.
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It's the same analysis, but based on the primary, there wasn't a significant difference between the two arms.
BY ATTORNEY DAVIES:
Q. Why do you believe that there was a significant difference if analasized using the UCSD shortness of breath questionnaire when there was not with the St. George's respiratory questionnaire in this study?
ATTORNEY DYKHUIS: Object to form, foundation.
THE WITNESS: They asked -- these are both what we call PROs, patient reported outcomes that ask very different questions. So it really depends on the questions that are asked and how the

patients answer them.
So it's entirely feasible that one can show a difference and the other one does not.
BY ATTORNEY DAVIES:
Q. Can you turn to Figure F5.
A. S5 or F5?
Q. S5, I mean. Still on Exhibit 7 in the appendix.
Do you see that?
A. I do.
Q. What is shown in Figure S5?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It's a change from baseline in FVC over time. And the two treatment arms Nintedanib --
(Reporter clarification)
THE WITNESS: The two treatment arms, the one is nintedanib plus Sildenafil, and the other one is Nintedanib plus placebo, and it's looking at FVC over time.
BY ATTORNEY DAVIES:
Q. Would you agree that Figure S5 shows

a difference in the change of FVC, which favors the combination of Sildenafil and Nintedanib as compared to Nintedanib and placebo alone?
ATTORNEY DYKHUIS: Object to the form and foundation.
THE WITNESS: At first glance I can see how you make the deduction, but you always have to contextualize it. But says this is hypothesis generating and it depends on how they did the analysis.
If you look at the number of patients at the bottom, you started out from the study, it was 137 versus 136. And then as the study progresses at 24 weeks, you have 109 versus 108.
So you had patients who dropped out, patients who didn't have data points to record. Which raises a whole lot of questions about what you see in the draft. If you look at Nintedanib plus Sildenafil, that's 28 patients. How do they contribute to the FVC initially versus the end.
If these were the sickest patients who dropped out, those 28, if they

continued to 24 weeks, they would have dragged this curve down. So there are a lot of holes in this, and as I said, it's at best hypothesis-generating, but you have to contextualize it as a post hoc analysis. And my best summation is that this is hypothesis-generating.
BY ATTORNEY DAVIES:
Q. What is the hypothesis that it's generating?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That does Sildenafil have some kind of effects on fibrosis. But this is a far measure from proving anything. It just raises that question.
So once again, I don't know how that dealt with the dropouts. If they had imputed zero values, which some people do, and assume that there was zero that were no longer around if they died, would that have dragged the new curve all the way down?
So there are many different ways to deal with missing data, but when you see that -- I don't know what the percent

is, it's at least 20 percent of the patients have missing data and how that was dealt with can alter these curves pretty dramatically.

BY ATTORNEY DAVIES:

Q. Can you turn to Figure S7 in the appendix in Exhibit 7?

A. Yes.

Q. What's shown at Figure S7?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: This is change from baseline in brain natriuretic peptide at week 24 between the two groups in the Nintedanib plus Sildenafil arm, the antichromium P was reduced and in the treatment arm -- sorry, in the placebo arm it did go up, getting a difference there of minus 51.3.

I'm not sure if this is statistically significant or not. I'm not if they show that in the paper. It looks like the confidence intervals are really quite wide. So I'm not sure if it's of statistical significance or not. I know that they provided a P value to go

with this.

BY ATTORNEY DAVIES:

Q. What do you use levels of brain natriuretic peptide for in clinical studies you've participated in for PH?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: It's a blood test that's a biomarker, which usually reflects cardiac stress and strain. The higher the level, the more stress the heart is under, and the lower the level, the less stress the heart is in.

BY ATTORNEY DAVIES:

Q. So would you agree that Figure S7 shows that in the Nintedanib plus Sildenafil arm it showed less stress on the heart than the Nintedanib plus placebo alone?

ATTORNEY DYKHUIS: Object to form and foundation.

THE WITNESS: That is a test and see what they said about Figure 7. I'm just curious to see if it's statistically significant.

BY ATTORNEY DAVIES:

Q. Sure.

A. Let's see if I talk about S7 here.

(Pause)

A. I see on page 172 that I do talk about the BNP change of baseline. They didn't even provide a P value. I suspect that because it's speculative they weren't allowed to provide a P value. That is not a reason why there wouldn't be a P value here.

So I'm not sure if it was statistically significant or not. But actually you can figure it out because 95 percent confidence intervals are minus 85 to minus 17.6. So this isn't outside the confidence interval.

So my interpretation of this would be that it's not statistically significant. Hopefully I've got that the right way around.

Q. So you would agree it shows a change in the levels -- Figure S7 shows a change in the levels, but you can't say sitting here whether or not it was statistically significant; right?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: The 95 percent confidence intervals include the number minus 51. So my interpretation based on

this is that it wasn't statistically significant.

BY ATTORNEY DAVIES:

Q. So there's a difference, but it's not statistically significant?

A. Correct.

ATTORNEY DYKHUIS: Object to form.

Q. When was the first time that you were optimistic that you were going to get a good result out of the INCREASE trial?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I don't remember. When I saw the results.

BY ATTORNEY DAVIES:

Q. When was that again.

A. It was towards the end of February of 2020.

Q. When in your mind during disease progression does PH become a driver for treatment outcomes in PH-ILD patients?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: We don't know that. We hypothesize, though, that when it does occur it becomes the main driver of

outcomes compared to the underlying primary disease, but we don't know that for sure.
The two intersect so closely and kind of feed off one another that it's hard to unwind the two from one another is what I would say.
BY ATTORNEY DAVIES:
Q. You would agree that at some point there's an inflection point where PH becomes the driver of treatment outcomes rather than ILD; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It sounds like you've read a -- you've seen a document that I produced in a couple of journals where I show that exact figure of an inflection point where -- but that's hypothetical. I don't know that for sure.
BY ATTORNEY DAVIES:
Q. Okay. But you presented on that; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I presented on that

because it gives the concept, yes.
BY ATTORNEY DAVIES:
Q. So the idea that at some point the PH severity reaches a level that the treatment of the PH component becomes the driver for the treatment outcome. Is that what you're trying to convey by that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's possible.
BY ATTORNEY DAVIES:
Q. Okay. Do you agree with that sitting here today?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I think it's more complex than this or that. As I said, the two are so closely intertwined that it's hard to really figure out. But it's possible that the PH is what's driving the outcomes.
BY ATTORNEY DAVIES:
(Exhibit 8 was marked for identification.)
ATTORNEY DAVIES: I'm going to enter as Exhibit 8 a document titled United States Patent 10,716,793 bearing

UTC Bates numbers UTC_PH-ILD-009772 through -796. Exhibit 8.
Q. And Doctor, is this the '793 patent that you offer opinions on in your report?
A. Yes, it appears to be.
BY ATTORNEY DAVIES:
Q. Do you have any understanding as to whether the '793 patent -- the claims of the '793 patent claims a method of treating PH-ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: That is the last page in this Column 18. What it's claiming is a method of treating pulmonary hypertension. So in answer to your question, it states it there.
BY ATTORNEY DAVIES:
Q. So you would agree that it describes a method of --
A. Sorry, hang on one second.
Q. Go ahead.
A. A method of treating pulmonary hypertension, it doesn't say interstitial lung disease. So my error. It says a method of treating pulmonary hypertension.

Q. Okay. Do you understand that that method of treating pulmonary hypertension described in the '793 patent includes treatment of PH-ILD?
ATTORNEY DYKHUIS: Objection to form. Speaks for itself.
THE WITNESS: I think there is mentioned somewhere in the patent of treating pulmonary hypertension without being specific to the cause. So I would regard that as any form of pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. If you look at table 3. Let me know when you're there. Columns 13 and 14.
And do you see under the table there's some very small words where it's describing the patient characteristics, hemodynamic parameters and gas exchange values of baseline before challenged with inhalative proteinoids is the title of the table.
A. Yes, I see that.
Q. And the last little line at the bottom of the table refers to pulmonary fibrosis.
A. I see the F. I'm not seeing the legend to say that it's pulmonary fibrosis. Let me see.

Q. Do you see the words right before the F that say "pulmonary fibrosis"?
A. I see IOTF. I'm not seeing where it says "pulmonary fibrosis."
Q. So, Doctor, go below the table. The very last line there says, "Etiology of pulmonary hypertension was classified as," and then it gives a list of the types of pulmonary --
A. Yes.
Q. Do you see there that it refers to pulmonary fibrosis?
A. Yes.
Q. Do you understand that to be PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm looking at the pulmonary artery pressure in the top. But it doesn't say that this is the systolic pulmonary artery pressure, the mean pulmonary artery pressure.
So I'm a little uncertain. You can have a high systemic pulmonary pressure without having pulmonary hypertension. The PDR, I'm used to operating in wood units. You have to divide these numbers by 80 to see if they

have pulmonary hypertension.
But the PDRs do look quite high for the group as a whole. What I don't know, though, is if you look at -- let's assume all these patients -- let's assume some of these patients at least might have had pulmonary hypertension. I don't know how many of the four had pulmonary hypertension and what their pressures were.
So there's not enough clarity and granularity to this table to make any definitive contribution.
BY ATTORNEY DAVIES:
Q. Doctor, do you recall --
A. Let me make one more point. This is values at baseline before challenge with enolated proteinoids. It's just some baseline values of groups of patients from assumably three different studies. I'm assuming one, two and three refer to three-different studies.
Q. In your declaration, do you recall offering opinions that the '327 patent is not invalidated by the disclosure or claims of the '793 patent.

Do you recall offering those opinions?
A. I do.
Q. When you offered those opinions, did you, in your opinion, understand that the '793 patent covered a method of treating PH-ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It was treating any form of pulmonary hypertension, which does include PH associated with interstitial lung disease. But treating pulmonary hypertension is taking a pressure that's high and making it lower.
And what we don't know and what I've alluded to is if it can or will result in clinical benefit or if that can or will result in clinical harm and what that clinical benefit may or may not be if, indeed, there is a clinical benefit.
So treating pulmonary hypertension does not equate to treating the patient.
BY ATTORNEY DAVIES:
Q. So is it your opinion that there's not enough data provided in the '793 patent to convince you that it's directed to a method of

treating PH-ILD in a patient?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It does talk about treating PH-ILD in a patient, but it doesn't talk about treating the patient. It's saying the pressures are high, we're going to make them lower. What does that mean? Benefit arm neutral, we don't know.
BY ATTORNEY DAVIES:
Q. What data would you have expected to see in the '793 patent for you to conclude that -- you described treating a PH-ILD with inhaled trepostinil?
ATTORNEY DYKHUIS: Object to form. Speculation.
THE WITNESS: As I just said, it's providing a treatment to the patient. Whether the treatment will be beneficial to the patient is an unknown.
It also depends on your -- one's notion of what treatment is. Giving someone a medication is arguably treatment, but is it directed to the question or disease in hand. You need to

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make that connection. There's no connection here to having any clinical benefit for the patient, or it just says we have a drug, we'll take a drug, and we'll lower the pressures in the lung, and that's where it ends.
BY ATTORNEY DAVIES:
Q. So in your opinion, the '793 patent provides no evidence as to a clinical benefit for a patient following administration of an inhaled treprostinil; correct?
ATTORNEY DYKHUIS: Object to form. Lack of foundation.
THE WITNESS: That would be correct. I mean, there's no mention of any clinical consequence of treating a pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. If you look at Table 2, and that's at Column 11 in the '793 patent. Just let me know once you're there.
A. Yeah.
Q. And you see Table 2 has some hemodynamic parameters that compares placebo versus 30 micrograms treprostinil, 45 micrograms

treprostinil, and 60 micrograms treprostinil.
Do you see that?
A. Yes.
Q. And in your opinion, does Table 2 provide any evidence of actually treating the patients with inhaled treprostinil?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I see the -- once again, I'm uncertain if it's a systolic pulmonary artery pressure or the mean pulmonary artery pressure because they are different. I see the pressures do come down numerically. Whether that's statistically significant or not, I'm not sure.
BY ATTORNEY DAVIES:
Q. So you reading the '793 patent could not conclude anything about the treatment of a patient with inhaled treprostinil from the data provided in Table 2; correct?
ATTORNEY DYKHUIS: Objection to form. Mischaracterizes.
THE WITNESS: You can treat a patient with inhaled treprostinil, and

you can cause the pressures to come down. And this might be what you're looking at. Whether it's significant detriment or not, I'm uncertain. There's not enough there yet. So it is treating the pulmonary hypertension, but there's no mention of any kind of clinical benefit.
And, once again, sometimes taking the pressures down might impose harm in a patient rather than helping the patient.
BY ATTORNEY DAVIES:
Q. And what data would you have needed to be provided in the '793 patent to convince you that there was a clinical benefit based on administration of inhaled treprostinil in these patients?
ATTORNEY DYKHUIS: Objection to form. Speculation.
THE WITNESS: I would need to see the study. I don't know if a patent application is going to convince me that medication is of benefit. I need to see primary study, I think.
BY ATTORNEY DAVIES:
Q. Would you need a phase

3 placebo-controlled randomized trial to conclude that?
ATTORNEY DYKHUIS: Same objections.
THE WITNESS: Correct.
BY ATTORNEY DAVIES:
(Exhibit 9 was marked for identification.)
Q. This is going to be Exhibit -- Doctor, I'm entering as Exhibit 9 a document entitled United States patent 11,826,327 B2, bearing production Number UTC_PH-ILD_005310 through -5360.
And, Doctor, is Exhibit 9 the '327 patent that you discussed in your report, your declaration in this case?
A. It appears to be.
Q. Can you go to the claims of the '327 patent, and I'm going to ask you to have the '327 patent open to the claims at the end and also the '793 patent, which is Exhibit 8.
A. Okay.
Q. I want you to specifically look at the dosing that's described in Claim 1 of the '327 and the dosing that's described in Claim 1 of the

'793 patent. Just let me know if you've had an opportunity to do that.
A. So the '327 says an amount -- an effective amount of at least 50 micrograms up to a maximum accelerated dose, okay.
Now, go to the '793, that says effective comprises from 15 to 19.
Q. So Claim 1 of both the '327 patent and the '793 patent describe the use of at least 15 micrograms of inhaled treprostinil; correct?
ATTORNEY DYKHUIS: Object to the form.
THE WITNESS: Correct.
BY ATTORNEY DAVIES:
Q. And then do you see the '327 patent refers to a single administration event that comprises at least six micrograms per breath?
A. I see that.
Q. And the '793 patent, do you see it refers to one to three breaths?
A. I see that.
Q. Okay. If I administered -- and you agree that, for example, 18 micrograms would be between 15 and 90 in the '793 patent; correct?
ATTORNEY DYKHUIS: Object to form.

THE WITNESS: 18 doses between 15 and 19.
BY ATTORNEY DAVIES:
Q. And if I delivered 18 micrograms in accordance with the '793 patent of inhaled treprostinil in three breaths, how many micrograms per breath would I be administering under the '793 patent?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: I believe it would be three breaths.
BY ATTORNEY DAVIES:
Q. I'm sorry. If I delivered 18 micrograms -- 18 micrograms of inhaled treprostinil, according to the '793 patent, in three breaths, how many micrograms of treprostinil would I be delivering per breath?
ATTORNEY DYKHUIS: Objection to form. Incomplete hypothetical.
THE WITNESS: Do you want me to multiply 18 times three?
BY ATTORNEY DAVIES:
Q. I think it's 18 divided by three?
A. I said that. Six.

Q. Okay. I apologize. And '327 patent also describes the use of six micrograms per breath; correct?
ATTORNEY DYKHUIS: Objection to the form. Mischaracterizes.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. So you would agree that the dosing described in the '793 and the '327 of inhaled treprostinil covers the same dosing regime; correct?
ATTORNEY DYKHUIS: Objection to form. Mischaracterizes.
THE WITNESS: They appear to overlap. It seems to be limited in one and not limited in the other.
BY ATTORNEY DAVIES:
Q. But you would agree that they overlap; correct?
A. They overlap.
Q. Okay. Both in terms of the total amount delivered and the amount given per breath; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: They overlap.

BY ATTORNEY DAVIES:
Q. Do you see that '327 is directed to -- look at Claim 1. So Claim 1 is directed to a method of proof, improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.
Do you see that?
A. Yes, I do.
Q. Do you believe that Claim 1 of the '793 patent also includes a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's what it says.
ATTORNEY DYKHUIS: Sorry. I note my objection. My objection is to form and foundation.
BY ATTORNEY DAVIES:
Q. Both the '327 -- both Claim 1 of the '327 patent and Claim 1 of the '793 patent require the administration of inhaled treprostinil; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.

BY ATTORNEY DAVIES:
Q. I'm sorry, Doctor. I don't think your answer came through.
A. That's correct.
Q. The data that's described in the '327 patent, does this -- was this data from the INCREASE study?
ATTORNEY DYKHUIS: Object to the form. Foundation.
THE WITNESS: I'm not sure you can call it data. It's a claim that appears to reflect some of the findings from the INCREASE study.
BY ATTORNEY DAVIES:
Q. Maybe just let me be a little bit more particular.
So moving away from the claim, and if you just look through the '327 patent, there is a number of figures that provide resulting data. And then if you look in the specification, flipping through it again, there's data regarding treatment using inhaled treprostinil versus placebo.
Is it your understanding that this data in the '327 patent came from the INCREASE study?
ATTORNEY DYKHUIS: Objection to

form. Foundation.
THE WITNESS: Let me look.
There's a lot of data. I'm trying to be sure.
A lot of the data is from the INCREASE study, that was your question. I'm looking at something on Table 16, which is not from the INCREASE study. Unless there's other tables amongst the 2020 tables, that is from the INCREASE.
BY ATTORNEY DAVIES:
Q. So sitting here today, you can't say for certain one way or the other; is that fair?
ATTORNEY DYKHUIS: Object to form.
Q. I'll ask that again with the mic on.
So sitting here today, you're not sure one way or another the source of the data in the '327 patent, where it came from; correct?
A. It seems to be from a number of studies. I see Table 19 there's mention of the TRIUMPH study, for example. It could be increased TRIUMPH, and then I think the switch study -- I forget what it was called -- from Tyvaso ultrasonic nebulizer to Tyvaso DPI. There might be one table from there.

Q. I'm going to mark as Exhibit 10 an abstract bearing the number S343 entitled "Inhaled treprostinil in Group 3 pulmonary hypertension by Agarwal and AV Waxman" and bearing production number UTC_PH-ILD_9828.
(Exhibit 10 was marked for identification)
ATTORNEY DYKHUIS: Is this a good time for a break?
ATTORNEY DAVIES: That's fine.
BY ATTORNEY DAVIES:
Q. Let me just -- have you seen this before.
A. I have.
Q. Okay.
THE VIDEOGRAPHER: We are off the record at 13:57.
(Recess taken from 1:57 p.m. to 2:07 p.m.)
THE VIDEOGRAPHER: We are on the record at 2:07 p.m.
BY ATTORNEY DAVIES:
Q. Going back to the Exhibit 10, which is the Agarwal abstract. Do you have that in front of you?

A. Yes.
Q. Have you seen this abstract before?
A. Yes.
Q. Do you cite to this abstract in your declaration?
A. Yes, I do.
Q. What's the title of this abstract?
A. The title is "Inhaled trepostinil in Group 3 pulmonary hypertension."
Q. And PH-ILD is a Group 3 pulmonary hypertension?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That's correct.
BY ATTORNEY DAVIES:
Q. Do you know who AB Waxman is?
A. Yes, I do.
Q. Who is he?
A. Aaron Waxman. I'm not sure what his middle initial stands for.
Q. And he's an author on this abstract?
A. Yes, he is.
Q. Was he also on the steering committee for INCREASE?
A. Yes, he is.
ATTORNEY DYKHUIS: Object to form.

Q. Do you know Dr. Waxman?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I do.
BY ATTORNEY DAVIES:
Q. Would you consider him to be an expert in the treatment of PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I think he has expertise in this area.
BY ATTORNEY DAVIES:
Q. Who is M. Agarwal?
A. I don't know who M. Agarwal is.
Q. Do you see the statement in the second sentence of the Purpose says, "Inhaled treprostinil therapy is delivered directly to well-ventilated lung units, preserving VQ, and reducing undesirable alterations in perfusion."
Do you see that sentence?
A. Yes.
Q. Do you agree with that sentence?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: I would phrase it differently. I think that we theorize that this is something that might happen,

and it doesn't happen necessarily in every patient, but it's not definitive as to what happens.
BY ATTORNEY DAVIES:
Q. If you look under results in this abstract, what is the mean change in the six-minute walk distance that's reported for the group who were administered inhaled treprostinil?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: The mean change in the six-minute walk distance was 60.85 meters with what looks like a standard deviation of 92.6 meters.
BY ATTORNEY DAVIES:
Q. And was that a statistically significant improvement?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Based on the P value, it does appear to be statistically significant.
BY ATTORNEY DAVIES:
Q. And the author concluded in this abstract that Group 3 PH can be effectively and safely treated with inhaled treprostinil.
Do you see that?

A. That's what's written in the conclusion.
Q. Do you see the Methods discussion?
A. I see the Methods section, yes.
Q. And do you see it describes the dosing starting at three breaths of inhaled treprostinil?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, I've seen it.
BY ATTORNEY DAVIES:
Q. And it's increased to a goal of 9 to 12 breaths four times daily as tolerated.
Do you see that?
A. I do see that.
Q. And you would agree that the dosing of inhaled treprostinil described here overlaps with the dosing described in Claim 1 of the '327 patent; right?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: Yes, I do.
BY ATTORNEY DAVIES:
Q. You can put that exhibit aside.
A. Can I make a comment?
Q. You can make a comment if you need

to.
A. I do note here that the pulmonary vascular resistance of the group was 8.7, which is very high. And in this group of patients without having further details about their lung disease, they could potentially be regarded as, you know, more than Group 1 PAH phenotype based on the very high pulmonary vascular resistance, which is different to the mean pulmonary vascular resistance of the patients which entered the INCREASE study which is around four, if I remember correctly.
So to your point about phenotypes, it appears to be a phenotype with more severe pulmonary hypertension that could be more successfully treated based on this abstract.
Q. But you would agree that the patients in this abstract would have included PH-ILD, you're saying a different subset from those that you examined in INCREASE?
ATTORNEY DYKHUIS: Object to form. Mischaracterizes.
THE WITNESS: They were -- I want to see the number. They called them restrictive disease. There's a difference between restrictive disease

and interstitial lung disease, which goes to what restriction is in patients who have restricted lung physiology and have reduced FVCs, which could be interstitial lung disease. But there are other things that could give restriction like if you have muscle weakness or if you have tremendous obesity, it can also manifest as restrictive disease. But I would assume for all intents and purposes that most, if not all of these patients, did have interstitial lung disease.
BY ATTORNEY DAVIES:
Q. I'm going to enter as Exhibit 11 New England Journal of Medicine article entitled "Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease" published in 2021, first author Waxman, last author Steven D. Nathan, M.D., bearing production number UTC_PH-ILD_010790 through -829.
Pass to you, Doctor.
(Exhibit 11 was marked for identification.)
Q. Doctor, what is Exhibit 11?
A. Exhibit 11 is a reproduction of a

study entitled, "Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease" that was published in the New England Journal of Medicine reflecting the results of the INCREASE study.
Q. And Doctor, you mentioned earlier that -- a change in FVC that was observed during the INCREASE study. Can you point me to where in this publication that's described?
A. As I recall, and it's been a while, it might just be in the supplements. Let me go straight there and see if I can find it -- I can find it.
Q. Doctor, if you go to Table S2, and you can look at whatever you want, but if you go to Table S2, the supplement, it's page 21 of the supplement, does that describe a change in FVC?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It does. No. Hang on a second. This is baseline characteristics so it doesn't. Let's move on.
Give me one minute. It looks like it could be in S6. S6, this looks like it. So what we see at week 16 is a

difference in percent predicted at 1.8, which was statistically significant at .03.
BY ATTORNEY DAVIES:
Q. Doctor, which page is that on?
A. I'm sorry, it's page 26, Table S6.
Q. You're looking at --
A. At the top you can see FVC and MLs and FVC in percent predicted.
Q. So with respect to FVC MLs, was there a difference between the treatment group and the inhaled treprostinil group? I'm sorry. Let me try that again.
With respect to FVC milliliters, was there a difference between the group given inhaled treprostinil versus the placebo group?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It was a numeric difference of 44.4 MLs, but it wasn't statistically significant with a P value of 1.21.
BY ATTORNEY DAVIES:
Q. And with respect to the change in FVC percent predicted, was there a difference between the treprostinil treatment group and the

placebo group?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: There was a difference of 1.8 percent, which was significant with a P value of .03 at 16 weeks.
BY ATTORNEY DAVIES:
Q. Do you see if you go to the page 326, so out of the supplement but back into the article itself, and I'm looking at page 326. Just let me know once you're there.
A. Yes, I'm there.
Q. Do you see the statement, it's pretty close to the Methods section at the bottom that says, "The data from previously completed pilot studies suggest that inhaled trepostinil could improve hemodynamics and functional capacity in patients with Group 3 pulmonary hypertension."
Do you see that?
A. I do.
Q. And there's references 9 through 12 that are cited there?
A. Yes.
Q. If you go to the references in the last page of the article. Are you there?

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A. I am.
Q. And reference 10 refers to an abstract by Agarwal and Waxman. Is that the Agarwal abstract that we've been talking about?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes, it appears to be.
BY ATTORNEY DAVIES:
Q. And for that statement you also relied on a publication by Faria-Urbina entitled "Inhaled Trepostinil and Pulmonary Hypertension Associated with Lung Disease."
Do you see that?
A. I do see that.
Q. Do you agree that you also cited to and relied on a publication by Bajwa, et al, entitled "The Safety and Tolerability of Inhaled Trepostinil in Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease" published in circulation in 2017?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I see that.
Q. And you also relied on a publication by Wang et al entitled "Hemodynamic and Gas Exchange Effects of Inhaled iloprost in patients

with COPD and Pulmonary Hypertension" published in the International Journal of Chronic Obstructive Pulmonary Disorders in 2017.
Do you see that?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I do see that.
BY ATTORNEY DAVIES:
Q. Are there any errors in this New England Journal of Medicine article that you're aware of sitting here today?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: I'm not aware of any errors, but if I may comment on those references.
It looks like the paper number 9, a lot of times when you have this, you have an abstract first, you present it at international meeting followed by a paper.
So I'm not sure how many of the same patients that were in 10 carried over to 9. There's a chance that this is a report on the same paper -- patients, just that one was reported as an abstract

and the other as a manuscript, and that's not uncommon. The statement that you read is data from previously computed --
(Reporter admonition)
THE WITNESS: Going back to the statement you previously read, data from previously completed pilot studies suggest that inhaled trepostinil can improve hemodynamics and functional capacity inpatients with Group 3 pulmonary hypertension.
Two of these papers, the last two appears to be COPD, which is another form of Group 3 pulmonary hypertension. So the reference really to this kind of improvement, this comes back to that one group of patients for the most part in terms of ILD.
BY ATTORNEY DAVIES:
Q. Those are the group of patients that you believe are described in both the Faria-Urbina publication and the Waxman abstract, which is Exhibit -- the Waxman-Agarwal abstract which is Exhibit 10 that we've introduced already; correct?
ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Yes, I'm not a hundred percent certain about it, but without having that paper and knowing exactly that it's the same patients, but that's what I suspect because it's not uncommon to have an abstract first followed by a full manuscript.
BY ATTORNEY DAVIES:
Q. Okay, Doctor. So I'm going to enter three exhibits. The first is Exhibit 12, which if you to the flip to the second page is entitled "Highlights of Prescribing Information" From Tyvaso treprostinil inhalation solution, revised July 2009 and bearing production number UTC_PH-ILD_010692 to -708.
(Exhibit 12 was marked for identification.)
Q. I'm going to also introduce as Exhibit 13 a document entitled "Highlights of Prescribing Information" Tyvaso, treprostinil inhalation solution revised both 03/2021 bearing Bates number UTC_PH-ILD_010744 through-758.
(Exhibit 13 was marked for identification.)
Q. And the last one, Exhibit 14. If

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you turn to the second page after the exhibit cover, it is entitled Highlights of Prescriptions information, Tyvaso DPI for oral administration, revised 06/2023 and bearing production numbers UTC_PH-ILD_010727 through -742. I'll pass these over to you.
And let me know when you've had a chance to look at them.
(Exhibit 14 was marked for identification.)
Q. There should be three there. So Exhibit 12 was the Tyvaso 2009 label.
A. Okay.
ATTORNEY DAVIES: It says Exhibit 2 on the front. That's how you guys cite it in the report.
ATTORNEY DYKHUIS: So 2009.
BY ATTORNEY DAVIES:
Q. 2009 is Exhibit 12. The 2021 label is Exhibit 13. And the Tyvaso DPI 23 label is 14.
Have you had a chance to look at them, Doctor?
A. Oh, gosh, do you want me to read all of them, or are you going to direct me where to go?
Q. And with respect to Exhibit 12, do

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you recognize that as the Tyvaso 2009 label for nebulized inhaled Tyvaso?
ATTORNEY DYKHUIS: Object to form.
Q. And I'll point you to the next page on the second page is the July 2009.
A. Yes, I do.
Q. And with respect to Exhibit 13, do you agree that that is the 2021 label for nebulized Tyvaso inhalation solution?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. For Exhibit 14, do you agree that 14 is the 2023 label for the Tyvaso DPI product?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Yes.
BY ATTORNEY DAVIES:
Q. So if you go to the -- let's go to -- sorry. Exhibits 12, 13, and 14 you'll recall are all cited in your declaration in this case; correct?
A. I'm sure they probably were, and I feel like I'll need to double check. But if you tell me that they were, then I'm good with that.

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Q. If you would like to double-check, that's totally fine.
A. I believe that they were.
Q. Okay. Going to Exhibit 12, what indication was Tyvaso approved for in 2009 in Exhibit 12?
A. It was approved for WHO Group 1 pulmonary arterial hypertension and NYHA Class III symptoms.
Q. In 2009, was Tyvaso approved for treatment of PH-ILD?
A. No, it wasn't.
Q. Okay. Can you turn to Exhibit 13, the 2021 Tyvaso label.
A. Yes. (Witness complies with request.)
Q. Just let me know once you're there.
A. I'm there.
Q. What was Tyvaso approved for in 2021 in the 2021 label of Exhibit 13?
A. So the difference in the two labels is that in addition to Group 1 PAH, Tyvaso was then approved in 2021 for pulmonary hypertension associated with interstitial lung disease -- that's PH-ILD -- to improve exercisability.

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Q. If you look at the dosing section of the 2021 label, you'll agree that the same dosing is used for treatment of both PAH Group 1 and PH-ILD Group 3; correct?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: That appears to be the case, yes.
BY ATTORNEY DAVIES:
Q. And you agree that the dosing of inhaled trepostinil in the 2021 Tyvaso label is the same dosing administration described in the 2009 label for nebulized Tyvaso; correct?
ATTORNEY DYKHUIS: Objection to form. Foundation.
THE WITNESS: Let me double-check that. I'm not seeing specific reference to 9 to 12 breaths, yeah, as the recommended dose unless I'm missing it. It gives a dosing table. Sorry, that's the DPI. I'm sorry.
BY ATTORNEY DAVIES:
Q. No problem. I can ask my question again, if that would be helpful.
Do you agree that the dosing of inhaled

trepostinil in the 2021 Tyvaso label is the same dosing administration described in the 2009 label for nebulized Tyvaso; correct?
ATTORNEY DYKHUIS: Object to form and vague.
THE WITNESS: What I'm seeing in the 2009 is maximum recommended dose is nine breaths of Tyvaso four times a day. It says 9 to 12 breaths. So it's not exactly the same.
BY ATTORNEY DAVIES:
Q. Have you changed the way that you dose Tyvaso to PH patients as compared to 2009?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I wouldn't say so. I didn't use much Tyvaso for PAH. So limited experience for PAH, but certainly a lot of experience with PH-ILD, where typically I'll try and get them to at least nine and preferably 12. And even though that's a dosing recommendation, sometimes we go beyond there.
BY ATTORNEY DAVIES:
Q. If you go to the 2009 label and go to page 2 at Section 2.1.

A. Okay.
Q. And do you see there there's a reference to the Tyvaso inhalation system?
A. Yes.
Q. And it's referred to as the OPTINEB-ir model ON-100/7.
Do you see that?
A. I do see that.
Q. Do you see there that at least the label describes it as a pulse delivery device?
A. I do see that, yes.
Q. Okay. And that's different than your understanding earlier in the day when you understood the nebulized device to be not a pulse delivery device; correct?
A. Yeah, that was my mistake.
Q. If you go to Exhibit 14, which is the DPI label.
A. (Witness complies with request.)
Yes.
Q. And in the 2023 label for Tyvaso DPI, what is Tyvaso DPI approved for?
A. It's approved for the treatment of pulmonary arterial hypertension as well as pulmonary hypertension associated with interstitial

lung disease.
Q. And if you look at the dosing and administration section in the 2023 Tyvaso DPI label, do you agree that the same dosing and administration is used for both of those two indications; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It appears to be so.
BY ATTORNEY DAVIES:
Q. Doctor, I'm going to enter as Exhibit 15 an article from Pulmonary Circulation entitled "The safety and Tolerability of Inhaled Trepostinil in Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease," first author Aboobacker A. Bajwa bearing Bates number UTC_PH-ILD_009844 through -9852.
Doctor, have you seen this paper before.
(Exhibit 15 was marked for identification.)
A. Let me see if I reference that. I don't recall. Oh, yeah, here we go, yeah.
Q. And Doctor, do you recall that this was also one of the publications that was cited in your INCREASE paper as a rationale for the study?
ATTORNEY DYKHUIS: Object to form.

Foundation.
THE WITNESS: It was part of the background. Once again, this is COPD versus ILD, which are entirely different.
BY ATTORNEY DAVIES:
Q. You as the author, though, did cite it in that INCREASE study publication; correct?
A. Correct, as background for potential treatment of Group 3 pulmonary hypertension, not for potential treatment of PH-ILD. And just to contextualize it, even though it's COPD, subsequently inhaled trepostinil has been shown not to work in PH associated with COPD.
Q. In your opinion, does this publication justify using inhaled trepostinil for PH-ILD or not?
ATTORNEY DYKHUIS: Object to form and foundation.
THE WITNESS: No, it does not.
BY ATTORNEY DAVIES:
Q. Does this paper form any part of the rationale, in your opinion, for the use of inhaled trepostinil in treating PH-ILD?
ATTORNEY DYKHUIS: Same objection.
THE WITNESS: It formed the

rationale for studying therapies for Group 3 pulmonary hypertension, which includes both ILD and COPD.
So the concept of treating pulmonary hypertension associated with lung disease was supported, but this was somewhat tangential to ILD because this was COPD, a totally different disease.
BY ATTORNEY DAVIES:
Q. I'm going to enter as Exhibit 16 a publication entitled "Inhaled Treprostinil and Pulmonary Hypertension Associated with Lung Disease," first author Mariana Faria-Urbina, last author Aaron B. Waxman bearing Bates number UTC_PH-ILD_009936 through -09943.
(Exhibit 16 was marked for identification.)
Q. Have you seen this paper before, Doctor?
A. I have seen it before, but I don't believe I saw it in the context of my declaration, but I could be wrong. Let me double-check that.
Sorry. Yes, so it was part of the volume of material that I considered for my declaration.
Q. And this also is one of the

publications that you as an author in the New England Journal of Medicine article for the INCREASE trial cited as rationale for that INCREASE study; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That is correct.
Part of the foundation for looking at the therapies in Group 3 pulmonary hypertension, yes.
BY ATTORNEY DAVIES:
Q. And this article at what is Exhibit 16 by Faria-Urbina, how did this form the foundation for the INCREASE study?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It provided proof of concept. It was hypothesis-generating that we actually could treat pulmonary hypertension associated with Group 3 with inhaled treprostinil.
BY ATTORNEY DAVIES:
Q. And, in fact, if you look at the results -- strike that.
You would agree that the patient population described in Exhibit 16 in the Faria-Urbina article

includes PH-ILD; correct?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: Yes, it did.
BY ATTORNEY DAVIES:
Q. Your response was "Yes, it did," Doctor; is that correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: I'm double-checking to see exactly what they said with regards to the population, but I'm sure that it did. I just want to see how they state the patients with ILD, how they presented them.
Well, in Table 1 they have inhaled treprostinil as nine of the patients. An additional five with combined pulmonary fibrosis and emphysema.
BY ATTORNEY DAVIES:
Q. So you would agree that the patient population in Faria-Urbina does include PH-ILD patients; correct?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Correct.

BY ATTORNEY DAVIES:
Q. And if you look at the results on the first page, the authors report a significant improvement in both functional class and six-minute walk distance.
Do you see that?
A. I do.
Q. And that improvement in six-minute walk distance for patients treated with inhaled trepostinil, is that statistically significant?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: It has a P value of .022, which would qualify it as statistically significant.
However, N equals 11, and there were 17 -- 22 patients. So I'm not sure who those 11 patients are they're reporting on. There were 14 and how many of them had interstitial lung disease versus the other condition.
BY ATTORNEY DAVIES:
Q. In your opinion, does this -- this paper in Exhibit 16, does this provide a justification to use inhaled trepostinil for the treatment of PH-ILD patients?

A. No, not at all. Not at all.
Q. Not at all?
A. No.
Q. Why not?
A. It's a retrospective study. So arguably there's some bias to retrospective papers. I did point out previously that the pulmonary vascular resistance was quite high and the pulmonary artery pressure was quite high.
So these were the patients who were leaning more to Group 1 PH-ILD phenotype. And then whenever you have a retrospective study, you are limited in terms of missing data, and I pointed that out that they reported on the six-minute walk distance of only 11 out of 22 patients. So what happened to the other half and what did they do. How did they treat their members.
So I think for all those reasons retrospective, missing data, this is hypothesis-generating. Even the authors themselves say the potential role of PH-specific drugs in Group 3 PH should be further assessed in the larger retrospective study. So they recognize their limitations.
Q. Do you know whether Dr. Waxman

considered this paper to provide a justification for the INCREASE study?
ATTORNEY DYKHUIS: Object to form. Calls for speculation.
THE WITNESS: I don't know for sure, but I suspect he did.
BY ATTORNEY DAVIES:
Q. Did you ever discuss this paper with Dr. Waxman?
A. I did not.
Q. Why do you suspect that he did believe this was a justification?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: Because he had the study. He had the experience of the individual patients, and so I'm sure that he ultimately believed this was a justification for an INCREASE study.
And I also believe that there was a justification for the PERFECT study. One worked for out great for ILD, the other one didn't work great for COPD using the same paper as justification.
So one went in a positive direction, the other one went to a

negative direction, which underscores the point that I made earlier which is that you cannot use this paper as a justification for treating PH as in the context of pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. I'm going to enter as Exhibit 17 a paper entitled "Hemodynamic and Gas Exchange Effects on Inhaled iloprost in patients with COPD, Pulmonary Hypertension" by Lan Wang, et al, published in the International Journal of COPD bearing production Number UTC_PH-ILD_010782 through -789.
Doctor, have you seen this paper before?
(Exhibit 17 was marked for identification.)
A. Let me see. Sorry.
ATTORNEY DYKHUIS: Excuse me. Could I have a copy?
Q. We're asking you to do a lot. That's normally not part of your job doing a deposition, but you're doing fine.
A. I preface that, I'm not as sharp as I should be because of this nagging cold and my nasal stuffiness.

Let me see if this is one of the cited references from my report. So this is Wang. Indeed it was.
Q. And this was also one of the publications that we looked at earlier that you had cited to in your New England Journal of Medicine INCREASE study publication for support for the rationale of that study; correct?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: That's correct.
BY ATTORNEY DAVIES:
Q. In your opinion, does this Wang 2017 paper provide a justification for using inhaled trepostinil to treat PH-ILD?
A. No, not at all.
Q. Why not?
A. Because this isn't PH-ILD. This is PH COPD.
Q. Do you know any of the authors of this study?
A. I do not.
Q. Did you ever discuss this study with any of the other members of the steering committee for the INCREASE study?

A. I did not. I don't recall discussing this paper at all.
Q. Do you believe that this study provides a justification for using inhaled trepostinil in a Group 3 patient population?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No. Not at all. It's a totally different drug. It's iloprost, not treprostinil. Given by a different system. If you have a different drug or a different drug formulation given by a different system, the results can be entirely different than what has been seen or what might be seen with another drug.
BY ATTORNEY DAVIES:
Q. Do you believe that this publication provides any justification for using a Group 1 PH therapy in a Group 3 PH patient?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: It does appear to be a reduction in the pulmonary pressures is as much as I can say. Four patients received a single dose of iloprost; it's

a nasal dilator. Then there's a bunch of things including the mean pulmonary arterial pressure and the pulmonary vascular resistance and it went down.
So what that means is the drug did what it's supposed to do. It's a pulmonary vasodilator with one dose. It has no meaning in terms of clinical benefit, and there's no long-term data here.
So this just is very, very -- just adds to the existing literature of what we knew already.
BY ATTORNEY DAVIES:
Q. Can you go back to Exhibit 15, which is the Bajwa article.
A. (Witness complies with request.) Okay.
Q. Are you there?
A. Yes, sir.
Q. In your opinion, does the Bajwa 2017 article at Exhibit 15 provide any justification for the use of a Group 1 PH treatment in the treatment of Group 3 PH?
ATTORNEY DYKHUIS: Objection to

form and foundation.
THE WITNESS: No, it doesn't. It's the same onset, provides a rationale, perhaps, to chase the hypothesis of inhaled trepostinil, and in this case specifically in COPD. But I don't believe that this particular series had any ILD patients.
So as I said earlier, this was cited in NJM article for Group 3 as a whole, which includes COPD and ILD. This by itself doesn't really provide justification for treating PH-ILD. It provides a rationale for studying inhaled trepostinil in PA COPD. That study was done and unfortunately was a negative study. And that was a PERFECT study.
BY ATTORNEY DAVIES:
(Exhibit 18 was marked for identification.)
(Discussion held off the record.)
Q. Dr. Nathan, I've given you what I've marked as Exhibit 18, a document titled "Safety and Tolerability of High-dose Inhaled Trepostinil in

Pulmonary Hypertension," first author Kishan Parikh bearing production number UTC_PH-ILD_ 010599 through -610.
Have you seen this publication before, Doctor?
A. Yes, I have.
Q. And this is the Parikh article that you discussed in your declaration; is that correct?
A. That's correct.
Q. In your opinion, does the Parikh article provide any justification for the use of inhaled trepostinil in the treatment of PH-ILD?
A. No, it does not.
ATTORNEY DYKHUIS: Object to form.
Q. Why not?
A. Because there's no evidence of any efficacy of clinical improvement, or their primary endpoint was that it was safe and tolerable. But there, once again, are holes in any study that's retrospective and single-centered.
So basically it's just going back through I don't know how many charts in cobbling the data together and putting this paper together. For that very reason all I can say is it was safe and tolerable but there's no evidence of efficacy.

If you look, for example, there were a total of 80 patients, 31 -- 32 percent -- 31.6 to be exact, had PH secondary to lung disease. 31.6. Then if you're looking for any efficacy measure, they do report the six-minute walk at follow-up visits one and two.

There's no set time interval. This is just the average time interval, 5.2 minutes is a wide range, and 20 minutes was an even wider range. And let's see what they said for the walk distance.

Something in here. Efficacy, six-minute walk, okay. Average change was 3.9 X from baseline to follow app. Out of 80 patients, there were 39. So what happened to the other 41? Did that drop out all the patients with PH ILD? We have no idea.

These could all be patients with PH, for all we know. And 31.6 meters sounds great, but what happened to the risk of the dropouts and who were the patients who dropped out and who were the ones that were included?

So there's always inherent bias to a retrospective study. Obviously the patients who we followed up on are the ones probably going to stick on the drug and probably going to do well. So there's inherent bias to the patients who were less

than 50 percent, and here we have I think 34 patients out of 80 who managed to stick on drug and eventually eke out -- not eke out, have a difference in the six-minute walks of 31.6 meters.

But that's why you need the randomized control studies to account for the patients who drop out, the patients who die, and for the patients to be blinded to therapy.

If we go back to the INCREASE study, there were patients in the placebo arms who had improvements in their numbers. So we don't know, once again, if this is a drug effect or if this is something else that's going on in these patients. We don't know how many of these patients went into pulmonary rehab, for example.

Pulmonary rehab will improve the six-minute walk distance. That's why you need the rigors of a randomized control study where patients can't leave. They can't initiate pulmonary rehab during the course of the study. So this really is totally uninformative in terms of efficacy.

Q. Do you know any of the authors on the Parikh publication in Exhibit 18?

A. I do. I know Victor Tapson. He was one of the steering committee members together with

myself and Aaron Waxman. And I do know Abby Poms.

Q. Do you know whether Dr. Tapson believed that this article formed a justification for the use of inhaled trepostinil in PH-ILD?

ATTORNEY DYKHUIS: Object to form. Speculation.

THE WITNESS: I can't speak for him. There's a good chance that he might have. I don't know.

BY ATTORNEY DAVIES:

Q. Did you ever talk to -- strike that. Who is Abbe D. Poms?

A. Abby Poms is a coordinator there. I think she is involved in the pulmonary rehab program at Duke. I'm not sure if she's still at Duke or not.

Can I take that back. I think she's the pulmonary hypertension coordinator at Duke or was.

Q. That's Abby Poms?

A. Abby Poms, yes.

Q. Do you know if United Therapeutics funded this study at Exhibit 18, the Parikh publication?

ATTORNEY DYKHUIS: Objection to form and foundation.

THE WITNESS: It does say at the end, Acknowledgments, that it was funded by United Therapeutics as well as an NIH grant.

BY ATTORNEY DAVIES:

Q. I'm introducing as Exhibit 19 a document entitled "United States Patent Application publication" to Wade et al, Publication Number U.S. 2013/0096200 A1 and bearing production numbers UTC_PH-ILD_010774 through -781.

(Exhibit 19 was marked for identification.)

Q. My first question, and I see you're already looking, is have you seen this document before?

A. Yes, I have.

Q. And is this one of the documents that you relied on in your declaration?

A. Yes, it is.

Q. Who was the applicant for this United States patent application?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: United Therapeutics Corporation.

BY ATTORNEY DAVIES:
Q. Then you see some inventors listed below there?
A. Uh-huh.
Q. Do you know Michael Wade?
A. I do not. I meet a lot of people. I might have met him at some point.
Q. Do you know Stewart Rich?
A. I do know Stewart Rich, yes.
Q. Who is Stewart Rich?
A. He's a PH expert and cardiologist in the Chicago area.
Q. Does he work for United Therapeutics?
A. At one point he did, but at this time I don't believe he does.
Q. Do you know Eugene Sullivan?
A. I do know Eugene Sullivan.
Q. Who is that?
A. He's a physician. I believe he's a pulmonologist by training. He used to be with FDA and then United Therapeutics, and now he's with another company.
Q. Do you know Robert Roscigno?
A. I do know Robert Roscigno, yes.

Q. Who is Robert Roscigno?
A. He used to have been with United Therapeutics, and he's moved around a little bit. I know that he has Liquidia -- with Liquidia and I'm not sure currently, it was a while ago that I knew him. I haven't seen him for a long time.
Q. Have you ever worked with Robert Roscigno?
A. I've never worked directly with him, no.
Q. Have you ever been involved in any clinical studies with Robert Roscigno?
A. Not that I recall. As you can tell from my CV when you went through it, there was some funding from UT many few years ago. I can't remember when exactly I met him. And it was involving a study somewhere.
Q. Do you know Roger Jeffs?
A. I do know Roger Jeffs, yes.
Q. Who is Roger Jeffs?
A. Roger Jeffs is the former CEO of United Therapeutics and to my understanding the current CEO of Liquidia.
Q. If you flip over to, I guess, page 1 of this application and look at the -- do you see

the heading "Field" for paragraph 2?
A. Yes.
Q. And paragraph 2 states, "The invention relates to the use of treprostinils or its derivatives or pharmaceutically acceptable salt thereof to treat and/or prevent interstitial lung disease or asthma or a condition associated with interstitial lung disease or asthma."
Do you see that?
A. I do.
Q. Is PH-ILD a condition associated with interstitial lung disease?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Yes, it is.
BY ATTORNEY DAVIES:
Q. If you look at paragraph 17, let me know once you're there.
A. Yes.
Q. Okay. It states, "The current invention relates to therapies that enhance blood flow by increasing blood flow through smaller vessels and capillaries and are effective to treat and prevent interstitial lung disease or conditions associated with interstitial lung disease such as

pulmonary fibrosis."
Do you see that?
A. Yes.
Q. So do you understand this patent application be directed to treatments for conditions associated with interstitial lung disease including PH-ILD?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: Actually, I have a slightly different take on that, because when they say "such as pulmonary fibrosis," what they mean by "conditions associated with interstitial lung disease" appears to be conditions associated under the broad banner of interstitial lung disease.
Otherwise they might have said pulmonary hypertension, which is more like a complication rather than discrete clinical entities under the broad umbrella of interstitial lung disease.
BY ATTORNEY DAVIES:
Q. You understand that's just an example, though, and it doesn't limit the

associated conditions for interstitial lung disease, correct?

ATTORNEY DYKHUIS: Objection to form. Vague.

THE WITNESS: I do understand that, and they could have put other conditions like connective tissue-related pulmonary fibrosis, scleredema-related pulmonary fibrosis. So to me they -- I can understand when it says conditions associated with interstitial lung disease you can go one of two ways. Are they talking about condition under the banner of ILD or conditions associated as comorbidities with the ILD.

That seems like the broad group of conditions and the ILD that I can see how someone else might interpret this is well, maybe this could include pulmonary hypertension, but that wouldn't have been my interpretation of this. My interpretation would have been what I described.

BY ATTORNEY DAVIES:

Q. If you go to Paragraph 30.

A. Uh-huh.

Q. Do you see it says, "The present invention encompasses methods of using treprostinil or its derivatives or pharmaceutically acceptable salts thereof."

Do you see that?

A. I do.

Q. So this patent application is directed to the use of treprostinil as a treatment?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: Yes.

BY ATTORNEY DAVIES:

Q. If you go to Paragraph 37, it's on page 3, second column.

A. Okay.

Q. In Paragraph 37 it's describing some formulations of the invention.

Do you see that?

ATTORNEY DYKHUIS: Objection to form.

THE WITNESS: Yes, I do.

BY ATTORNEY DAVIES:

Q. And do you see one of the formulations of the invention that is described as

inhalation in solid and liquid form?

A. I see it.

Q. So you understand this patent to be describing the use of inhaled trepostinil in either solid or liquid forms as a treatment?

ATTORNEY DYKHUIS: Objection to form. Misstates.

THE WITNESS: Yes.

BY ATTORNEY DAVIES:

Q. Could you go to Example 4 on page 5 beginning with paragraph 61.

A. Okay.

Q. Here Example 4 refers to the effects of treprostinil, either in the form of Remodulin or inhaled, on patients analyzed using the six-minute walk test.

Do you see that?

A. I do.

Q. And then it goes on to describe the six-minute walk test as a standard assessment of exercise capacity and breathlessness in patients with lung disease.

Do you see that?

A. I do.

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: I do.

BY ATTORNEY DAVIES:

Q. Do you agree with that statement?

ATTORNEY DYKHUIS: Object to form.

THE WITNESS: Yes.

BY ATTORNEY DAVIES:

Q. So this patent application describes the assessment of inhaled trepostinil therapy using a six-minute walk test as an assessment of exercise capacity; correct?

ATTORNEY DYKHUIS: Object to form. Mischaracterizes.

THE WITNESS: It appears to be so.

BY ATTORNEY DAVIES:

Q. Doctor, can you look at Paragraph 82, which is Example 6 or the start of Example 6, I should say.

A. Okay.

Q. Just let me know once you're there.

A. Yes.

Q. So here it's describing, "The following study shows the vehicle of intravenous treprostinil in patients with idiopathic pulmonary fibrosis and pulmonary hypertension."

Do you see that?

A. I do.
Q. With that description in Paragraph 82, do you understand that this patent is, in fact, directed to PH including PH-ILD?
ATTORNEY DYKHUIS: Object to form. Form. Foundation. Speculative.
THE WITNESS: You know, I can't answer that because these are just examples. These are not specific claims, as far as I can tell. These are just 19 examples in the literature. So there's no specific claim here.
So if you look at this example, it's intravenous treprostinil anyway. Small segment of IPF for pulmonary hypertension. I guess I don't know if you're going to go to the claim, there's a claim, and this is beyond my realm of expertise in terms of how the patents are formulated and what they cover.
But there's mention put in this of many different things, and I'm not sure just because they mention it you can connect the dots in terms of what it covers.

BY ATTORNEY DAVIES:
Q. Can you go to Paragraph 50, Doctor, and that's back on page 4. And it's right before the Example section.
A. (Witness complies with request.)
Q. And Example 50 provides a description of what the examples are. It states, "The examples described herein are illustrative of present invention and are not intended to be limitations thereon."
Do you see that?
A. I do.
Q. So from what you understand the examples in the patent to actually be illustrations of the present inventions described in this patent?
ATTORNEY DYKHUIS: Object to form. Foundation and calls for a legal conclusion.
THE WITNESS: I think it's beyond my expertise to comment on that.
BY ATTORNEY DAVIES:
Q. PH IPH is a form of PH-ILD; right?
A. Yes.
Q. If you go to Paragraph 24 of this patent application description, let me know once

you're there.
A. Yeah.
Q. And Paragraph 24 states, "Many acute and chronic lung disorders with variable degrees of inflammation and fibrosis are collectively referred to as interstitial lung diseases. Because of the stiff fibrosis of the lung, pulmonary or arterial hypertension, PAH, is often a late complication of some forms of ILD."
Do you see that?
A. I do.
Q. Do you understand that to be describing PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: That actually doesn't. It's describing PAH, which is Group 1 pulmonary hypertension, and this goes to what I mentioned earlier that sometimes patients will develop what I would regard as pulmonary hypertension disproportionate to the extent of their lung disease, in which case I would regard them as having Group 1 pulmonary arterial hypertension. So that's what I mean.

BY ATTORNEY DAVIES:
Q. So if you have a patient with PAH as well as ILD complications, you would not consider that to be a PH-ILD patient. Is that correct?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: It goes down to where are you going to group the patient. And so to me, the way this reads is we're talking about ILD complicated by pulmonary hypertension or associated with pulmonary hypertension that is severe enough and out of proportion to the lung disease to be regarded as Group 1 PAH.
Any time you say "PAH," that defaults to Group 1. PH covers one to five, but PAH is purely Group 1.
BY ATTORNEY DAVIES:
Q. Do other people in the field view that distinction the same way as you, or is there a difference in opinions as to that point as to whether a patient with PAH and underlying ILD would be a PH-ILD patient or not?
ATTORNEY DYKHUIS: Objection to form. Speculation.

THE WITNESS: I think anyone who is familiar with the field of pulmonary hypertension knows and recognizes that distinction. You could catch someone who is not. It's a common misconception amongst people who go into pulmonary hypertension to talk about PAH and PH interchangeably, but not amongst people who know pulmonary hypertension.
If you say "PAH," you're referring to Group 1 pulmonary hypertension.
BY ATTORNEY DAVIES:
Q. Have you ever seen a patient in your clinical practice who you would consider to have -- who you would consider to have been suffering from both Group 1 PAH and Group 3 PH-ILD?
ATTORNEY DYKHUIS: Object to form.
THE WITNESS: No. That's a theoretic concept that's impossible to figure out. You either make the distinction that that is more of a Group 1 phenotype or this is Group 3. You can't say there's, you know, a little bit of three in some. It's impossible to thread that needle.

BY ATTORNEY DAVIES:
Q. How do you decide where the dividing line is between these patients?
A. That's a problem and one of a lot of debate. There are cases that are clearly Group 3, cases that are clearly Group 1, and there's a spectrum between them. And I think I've alluded to it earlier.
You look at the severity of the lung disease in relation to the severity of the hemodynamic impairment, and it becomes a subject of judgment call where they best reside, Group 1 or Group 3.
ATTORNEY DAVIES: Let's take a break if that's okay.
(Discussion held off the record.)
THE VIDEOGRAPHER: We are off the record at 15:18.
(Recess taken from 3:18 p.m. to 3:43 p.m.)
THE VIDEOGRAPHER: We are the record at 15:43.
BY ATTORNEY DAVIES:
Q. Welcome back, Dr. Nathan. At any of

the breaks today, did you have any discussions with counsel about your testimony?
A. No.
ATTORNEY DAVIES: Okay. I have no further questions, but obviously reserve the right to follow-up based on what you may or may not ask, Art.
EXAMINATION BY
ATTORNEY DYKHUIS:
Q. Dr. Nathan, I have a few questions for you.
Understanding you have not been feeling all that well today and wanted to clarify some of the testimony after lunch.
Do you recall some questions about the '793 patent claims and then how, if at all, they relate to improving exercise capacity?
ATTORNEY DAVIES: Objection. Form.
THE WITNESS: I do.
BY ATTORNEY DYKHUIS:
Q. Let's get out, it's Exhibit 8 and 9. You have a number in front of you. Find 8 and 9.
A. (Witness complies with request.)
Q. I think Exhibit 9 is the '327

patent; correct?
A. That's correct.
Q. Let's turn to the claim at the end if you would, please.
A. Okay.
Q. Can you look at Claim 1.
A. Yes.
Q. And Claim 1 recites a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease.
Do you see that?
ATTORNEY DAVIES: Objection. Form.
THE WITNESS: I do.
BY ATTORNEY DYKHUIS:
Q. So Claim 1 of the '327 patent involves explicitly improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease?
A. Yes.
ATTORNEY DAVIES: Objection. Form.
Q. Then if you can turn to the '793 patent, which is Exhibit 8.

A. Okay.
Q. And let's go to the claims of the '793 patent. Tell me when you've got those pulled up.
A. I'm here.
Q. Does Claim 1 of the '793 patent say -- have any words about improving exercise capacity?
A. No, it does not.
Q. Let's keep those two handy, but then your declaration is Exhibit 2. And then let's go to Paragraph 176, please.
A. Yes. I'm at 176.
Q. Did counsel direct you specifically to Paragraph 176 at all today?
ATTORNEY DAVIES: Objection. Form.
THE WITNESS: No.
BY ATTORNEY DAVIES:
Q. Could you read 176 just to yourself and let me know when you're finished.
ATTORNEY DAVIES: Same objection.
THE WITNESS: I remember now opining on this, that the '793 patent does not teach anything about what the

'327 patent has as its claim in terms of improving exercise tolerance, FVC and other things that are within the -327 claim.
BY ATTORNEY DYKHUIS:
Q. So why is it your opinion that the '793 patent doesn't teach anything about the '327 patent improving exercise capacity?
ATTORNEY DAVIES: Objection. Form.
THE WITNESS: There are a lot of examples thrown within it. I'm sorry. This is -- I was getting my patents confused. Let me start again.
The '793 patent, all that does is it talks about treating pulmonary hypertension. And treating pulmonary hypertension means taking pressures that are high within the lungs and making them lower.
There's no mention of any kind of clinical benefit in the original '793 patent, and that's what the '327 patent gets into.

BY ATTORNEY DYKHUIS:
Q. Okay. You can close your declaration there. And then you still have the '327 and '793 patent in front of you, Doctor?
A. '793 and '327, yes.
Q. Which one do you have on the left?
A. This is the '793.
Q. Could you open that '793 back to the claims again.
A. (Witness complies with request.) Okay.
Q. And I'd like to do a little side-by-side there. You can hold it if you like. I actually want to ask you about a specific question again in a moment.
A. Okay.
Q. So you were asked a question earlier, and I'm just going to read it.
"Do you believe that Claim 1 of the '793 patent also includes a method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease?"
There was an objection, and then you said, "That's what it says."
Do you recall that question and answer from

earlier today?
A. I don't recall specifically, but I told you wrong. I think that I was thinking about the '327 patent when that question was posed at me. So I apologize for getting the numbers confused. Clearly it does, which the '793 patent does not mention anything about improving exercise capacity, so that was not -- my mistake.
Q. So when you said "That's what it says," you were referring to the '327 patent?
ATTORNEY DAVIES: Objection. Form.
You can answer.
THE WITNESS: Yes, that's correct.
BY ATTORNEY DYKHUIS:
Q. I think on the left you have the '793 patent. Let's look at the cover page.
You were asked some questions earlier today about -- I think it was a conference of some sort where you were admonished publically over the RISE-IIP study?
A. That's correct.
Q. That was something that was in front of 500 people or so?
A. Yes.

Q. Who was it who was admonishing you?
A. It was Dr. Lewis Rubin.
Q. So on the cover of the '793 patent, do you see a section Inventors, and it lists a few people?
A. Yes.
Q. One of the inventors is Lewis J. Rubin?
A. Yes, indeed. It's the same person.
ATTORNEY DYKHUIS: No further questions.
EXAMINATION BY
ATTORNEY DAVIES::
Q. Just a couple additional questions for me, Doctor.
If you look back at the '793 patent at Claim 1, just let me know once you're there.
A. I'm there.
Q. Okay. So is it your opinion that Claim 1 of the '793 patent excludes a method of improving exercise capacity in a patient with PH-ILD?
ATTORNEY DYKHUIS: Object to form. Foundation.
THE WITNESS: Yes, it does.

BY ATTORNEY DAVIES:
Q. Counsel directed you to paragraph 176 of your declaration. Do you recall that?
A. I don't recall that.
Q. Can you go to paragraph 176 of your declaration.
A. Okay.
Q. Did you prepare paragraph 176 in your declaration, or was that prepared by counsel?
ATTORNEY DYKHUIS: Objection to form.
THE WITNESS: To be honest, I don't recall. We all had a hand in this declaration, and I don't recall who had the original version. It might have been counsel. There were many iterations going backwards and forwards. So I can't a hundred percent attest to that.
I certainly had a role in this in terms of editing, adding, and deleting things that I didn't think was necessary to make it my own words.
ATTORNEY DAVIES: We have no further questions at this time.

ATTORNEY DYKHUIS: No further questions for UTC.
THE VIDEOGRAPHER: We are off the record at 15:54.
(Proceedings adjourned at 3:54 p.m.)

DISTRICT OF COLUMBIA: SS

I, Barbara Moore, a Registered Court Reporter of the District of Columbia, do hereby certify that these proceedings took place before me at the time and place herein set out, and the proceedings were recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor an employee of counsel nor related to any of the parties, nor in any way interested in the outcome of this action.

____

BARBARA MOORE, CRR, RMR

____

My Commission Expires:
September 30, 2028

CERTIFICATE OF READING AND SIGNING

I, ______________________, the deponent herein, do hereby certify that I have read the foregoing deposition and certify that it is a true and accurate transcription of my testimony given in the above-captioned matter, except for any corrections as noted on the enclosed errata sheet.

____
STEVEN D. NATHAN

E-R-R-A-T-A

RE: UNITED THERAPEUTHE COURTICS v. LIQUIDIA

Enclosed is the transcript of your deposition testimony. Please review the transcript, complete and distribute the signed errata sheet and acknowledgment page to all parties, including this office, within 30 days. Any changes and/or corrections should be listed below and not made upon the transcript itself:

PAGE LINE CHANGE OR CORRECTION REASON

DATE_____________ SIGNATURE_______________
STEVEN NATHAN, M.D.

EXHIBIT 10

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,)
)
Plaintiff,)
) C.A. No. 20-755-RGA-JLH
v.)
) Volume III
LIQUIDIA TECHNOLOGIES, INC.,)
)
Defendant.)

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Wednesday, March 30, 2022
8:30 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: JACK B. BLUMENFELD, ESQUIRE
BY: MICHAEL J. FLYNN, ESQUIRE
BY: SARAH E. SIMONETTI, ESQUIRE

-and-

GOODWIN PROCTER LLP
BY: WILLIAM C. JACKSON, ESQUIRE
BY: HUIYA WU, ESQUIRE
BY: IAN B. BROOKS, ESQUIRE
BY: JOEL BROUSSARD, ESQUIRE
BY: HARRISON GUNN, ESQUIRE
BY: ERIC LEVI, ESQUIRE

- and -

APPEARANCES CONTINUED:

McDERMOTT WILL & EMERY LLP
BY: DOUGLAS H. CARSTEN, ESQUIRE
BY: ADAM W. BURROWBRIDGE, ESQUIRE
BY: KATHERINE PAPPAS, ESQUIRE
BY: TIMOTHY M. DUNKER, ESQUIRE
BY: ART P. DYKHUIS, ESQUIRE
BY: AMY MAHAN, ESQUIRE
BY: JOSHUA REVILLA, ESQUIRE
BY: JIAXIAO ZHANG, ESQUIRE

For the Plaintiffs

SHAW KELLER LLP
BY: KAREN E. KELLER, ESQUIRE
BY: NATHAN R. HOESCHEN, ESQUIRE
BY: EMILY DiBENEDETTO, ESQUIRE

-and-

COOLEY LLP
BY: SANYA SUKDUANG, ESQUIRE
BY: ADAM M. PIVOVAR, ESQUIRE
BY: BRITTANY CAZAKOFF, ESQUIRE
BY: DOUGLAS W. CHEEK, ESQUIRE
BY: JONATHAN R. DAVIES, ESQUIRE
BY: IVOR ELRIFI, ESQUIRE
BY: DEEPA KANNAPPAN, ESQUIRE
BY: LAUREN KRICKL, ESQUIRE
BY: ERIK B. MILCH, ESQUIRE
BY: KYUNG TAECK MINN, ESQUIRE

08:07:47 For the Defendants

08:07:47 08:07:47 *** PROCEEDINGS ***

08:29:49 08:29:50 DEPUTY CLERK: All rise. Court is now in

08:29:51 session. The Honorable Richard G. Andrews presiding.

08:29:56 THE COURT: All right. Good morning, please be

08:29:58 seated.

I'm not sure exactly what the order is here, but whoever is next, please do something.

MS. KIM: Good morning, Your Honor. Mandy Kim on behalf of UT. And we call Dr. Waxman to the stand.

MR. FLYNN: Your Honor, may I approach?

THE COURT: Sure.

DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: Aaron B. Waxman, A-A-R-O-N. Middle initial B. Last name W-A-X-M-A-N.

DEPUTY CLERK: Do you affirm that the testimony you are about to give to the Court in the case now pending will be the truth, the whole truth, and nothing but the truth, you do so affirm?

THE WITNESS: I do.

DEPUTY CLERK: Please speak in the microphone. Please make sure you speak into it.

THE COURT: Thank you.

MS. KIM: May I proceed, Your Honor?

THE COURT: Yes.

DIRECT EXAMINATION

BY MS. KIM:

Q. Good morning, Dr. Waxman. Please introduce yourself to the Court and what you do for a living.

A. My name is Aaron Waxman, and I'm a physician,

08:34:32 pulmonary critical care medicine, at the Brigham and Women's Hospital in Boston and Associate professor of medicine at Harvard Medical School. And I'm the executive director of the Center for Pulmonary Heart Disease and more specifically the director of the pulmonary vascular disease program at Brigham and Women's Hospital.

08:34:33 Q. What are your responsibilities in these positions?

08:34:33 A. So as the executive director, I oversee the broader pulmonary heart disease program, which includes all aspects of pulmonary vascular disease and right-heart failure and oversee eight faculty that work on the program as well as a large clinical trials and basic research program.

08:34:33 Q. Please briefly describe your educational background.

08:34:33 A. Undergraduate, I went to GW, George Washington University, in D.C. and then went on to get a Ph.D. in anatomy and neuroscience, and then after that, an M.D. at Yale University where I also did a number of research fellowships and then all my post-graduate training in internal medicine, pulmonary, and critical care medicine.

08:34:33 Q. And what area of medicine have you been focused on after medical school and fellowships?

08:34:33 A. Again, broadly speaking, I've practiced the full range of pulmonary and, specifically, critical care medicine and then more specifically pulmonary vascular disease and care of patients with pulmonary hypertension.

yes.

Q. So reading Claim 1 in the context of the patent, would a POSA, in your opinion, know whether isolated postcapillary PH is within the scope of the claims?

A. I think a POSA would understand that isolated postcapillary disease, again, would be treated with a diuretic and not a pulmonary vasodilator.

Q. As of May 2006, would a POSA have understood that prostacyclins would not be -- would not likely work for isolated postcapillary PH patients?

A. Yes. I mean, essentially, any pulmonary vasodilator would probably not be needed.

Q. Thank you. Let's turn to enablement. Have you prepared a slide of your opinions on enablement?

A. Yes.

Q. What are your opinions -- what are your -- at a high level, what are your opinions on enablement?

A. So, I think that the information provided in the patent provides plenty of information to enable someone who's skilled in the art to be able to make the invention.

Q. And what's the basis for your opinions?

A. Well, in the examples that are in the patent, there's plenty of information as far as the patient population to treat, how to treat, as far as a single-event therapeutic dosing that results in improved hemodynamics. There's

information about delivering it as an inhaled therapy, and there's information, I think very importantly, on dosing to get that single-event therapeutic dose.

Q. And do you recall Dr. Hill opining that, once again, a POSA or the patent is not enabled because -- he used the same rationale of isolated postcapillary group two PH patients not being enabled with the description in this patent?

Do you recall that?

A. I recall that, yes.

Q. Do you agree with his opinions?

A. Well, I think, again, as I've said, I don't agree in the sense that we wouldn't treat a postcapillary disease with a pulmonary vasodilator of any kind.

Q. And does the patent support your opinions?

A. I think it does. Like I said, there's a description in there of treating idiopathic or group one, group five with PH other, chronic thromboembolic, group four, pulmonary fibrosis, group three, and if we look at that table up there, it does describe pulmonary hypertension, but you can see there's no pulmonary capillary wedge pressure listed anywhere, so we really don't know if anyone had combined pre- or postcapillary PH.

Q. Do you recall Dr. Hill also opined that in 2006 there was no evidence that prostacyclins could treat any group two

Q. Could one expect for that to translate into therapeutic efficacy?

A. Well, that would speak to therapeutically effective dosing when you see a hemodynamic response. Yes.

Q. So, I want to briefly talk about one of the limitations in Claim 1, a therapeutically effective single-event dose. Can you explain to the Court what this term means.

A. So, a single event therapeutically effective dose refers to providing an effective dose of the drug in a single sitting.

Q. And in your opinion, can a single-event dose be therapeutically effective?

A. Well, especially in the case where we're talking about a hemodynamic disease, you want to see a therapeutically effective dose cause a positive change in those hemodynamics. So any anything - -- a therapeutically effective dose should cause a reduction in pulmonary artery pressure and cause a reduction in pulmonary vascular resistance, and one would expect then that that hemodynamic effect would translate into a patient feeling better, doing more, and probably living longer.

Q. Do you recall Dr. Hill's opinions in his expert report regarding what "therapeutic effective" means?

A. I do, yes.

Q. What are his opinions, to your understanding?

A. His opinions are that a therapeutically effective dose should make a patient feel better, do more, and live longer.

Q. Do you agree with Dr. Hill's opinions?

A. Well, I think those opinions are taken from an FDA mandate that came down, especially in pulmonary hypertension clinical trial development, where the goal of these drugs are to make patients feel better, live -- and do more and live longer. But that applies to a clinical trial.

But when we're talking about the clinically effective dose in a hemodynamic disease, it has to be able to improve the hemodynamics, which then would translate into all of those features: a patient feeling better, doing more, and living longer.

Q. Even if the Court were to agree with Dr. Hill's opinion with respect to therapeutically effective, in your opinion, does Liquidia's LIQ861 product still meet this claim limitation?

A. Yes. I mean, it's been compared nicely to TYVASO and has the same -- same therapeutically effective single-event dosing.

Q. Even just taking it once?

A. It -- taking it once impacts the hemodynamics in a positive way that would translate into those three features

that I mentioned, feeling better, doing more, and living longer.

Q. Thank you Dr. Waxman.

Let's move on to Claim 4. Can you explain to the Court what the basis for your opinions with respect to Claim 4 are.

A. Well, Claim 4 describes an inhalation device as a dry-powder inhaler. And I think it's very clear from all the documents we just reviewed that Liquidia 861 is a dry-powder inhaler.

Q. And I think you have a slide on that. Can you explain some of the highlights from the documents that you looked at right now with respect to Claim 4.

A. Yeah. As I said, all of the documents describe -- especially the package inserts and the instructions to the patient -- specifically describe a dry-powder oral inhalation and provide it has a dry-powder inhaler, and it also speaks to the single-event dosing.

Q. Thank you. Let's move on to dependent Claim 6.

Can you explain the basis for your opinions.

A. Yeah. Essentially, the same as Claim 4, in that this is simply talking about the administration as a powder, and we've just reviewed how it's not only a powder, it is a dry-powder delivered through a dry-powder inhaler, and it is obviously Treprostinil.

EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 20-755 (RGA)
	)	
LIQUIDIA TECHNOLOGIES, INC.,	)	
	)	
Defendant.	)	

<u>EXHIBIT 2: PLAINTIFF'S STATEMENT OF CONTESTED FACTS</u>

I. INTRODUCTION

In accordance with Local Rule 16.3(c)(3) of the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, Plaintiff United Therapeutics Corporation ("Plaintiff" or "UTC") submits the following statement of contested facts with respect to United States Patent Nos. 9,593,066 (the "'066 patent"); 9,604,901 (the "'901 patent"); and 10,716,793 (the "'793 patent") (collectively, the "Patents-in-Suit").

The following statements are meant to serve as an overview of the contested facts to be litigated at trial. Accordingly, Plaintiff reserves the right to prove additional details regarding the below facts, including any facts identified in its pleadings, discovery responses, including in its contentions, and/or expert reports and depositions, which Plaintiff incorporates by reference. Plaintiff further intends to offer evidence to rebut evidence offered by Defendant. Plaintiff reserves the right to modify or amend this Exhibit to the extent necessary to reflect any future rulings by the Court, and to supplement or amend this Exhibit to fairly respond to any new issues that Defendant may raise. To the extent Plaintiff's statement of the issues of law that remain to be litigated, which is submitted as Exhibit 4 hereto, contains issues of fact, those issues are incorporated herein by reference. Moreover, if any issue of fact identified below should properly be considered an issue of law, then such statement should be considered to be part of Plaintiff's statement of issues of law that remain to be litigated. Plaintiff incorporates by reference its expert reports in support of any proof to be presented by expert testimony.

II. THE PATENTS-IN-SUIT

1. Plaintiff is the lawful owner of the Patents-in-Suit by assignment of all right, title, and interest in and to the Patents-in-Suit, including the right to bring infringement suits.

III. FACTS PERTAINING TO INFRINGEMENT OF THE ’066 AND ’793 PATENTS

A. Defendant’s Proposed Product

2. On January 24, 2020, Defendant submitted New Drug Application (NDA) No. 213005 (“Defendant’s NDA”) under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the “505(b)(2) Application”) to the United States Food and Drug Administration (“FDA”) seeking approval, prior to the expiration of the ’066, ’901, and ’793 patents, to manufacture, market, and sell a copy (the “Proposed Product”) of Plaintiff’s TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/ml.

3. Defendant’s 505(b)(2) Application was submitted prior to the expiration date of the ’793 patent and the expiration date of the ’066 and ’901 patents.

4. Defendant’s 505(b)(2) Application contains a “Paragraph IV” certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) alleging that the ’066 and ’901 patents are invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale of Defendant’s Proposed Product.

5. In a “Notice Letter” dated April 24, 2020, Defendant informed Plaintiff that Defendant’s 505(b)(2) Application contained, *inter alia*, a Paragraph IV certification regarding the ’066 and ’901 patents.

6. Defendant’s Notice Letter further indicated that Defendant was seeking FDA approval to engage in the commercial manufacture, use, and/or sale of Defendant’s Proposed Product prior to the expiration of the ’066 and ’901 patents.

7. Plaintiff commenced this action before the expiration of forty-five days from the date it received Defendant’s Notice Letter.

8. Defendant’s Proposed Product is a dry powder formulation of treprostinil sodium

to be inhaled from a [redacted] Defendant's dry powder formulation is contained in capsules of [redacted] of treprostinil sodium. Two capsules can be combined to create larger doses, such as [redacted]

9. Defendant has imported and will import treprostinil sodium drug substance for use in Defendant's Proposed Product. The treprostinil sodium drug substance is manufactured by Yonsung Fine Chemicals Co., Ltd. ("Yonsung") in Korea. Yonsung manufactures treprostinil sodium drug substance according to Drug Master File ("DMF") No. 27680. Defendant's NDA cites Yonsung's DMF.

10. Defendant uses LGM Pharma as its broker and LGM Pharma ships treprostinil sodium from Yonsung to Defendant.

11. Defendant's Proposed Label describes Defendant's Proposed Product as [redacted]

12. Defendant's Proposed Label identifies the ingredients in Defendant's Proposed Product as: treprostinil (the active ingredient) [redacted]

13. Defendant's Proposed Label states that the [redacted]

14. [redacted]

15. The dry powder particles are [redacted]

[redacted]

16. The particles have an aerodynamic size of between [redacted] for the powder's mass median aerodynamic diameter.

17. The inhaler provided with Defendant's Proposed Product is an [redacted] dry powder inhaler (DPI) manufactured by [redacted]

18. [redacted]

19. Defendant's Proposed Product is provided to patients in a [redacted] which includes a LIQ861 dry powder inhaler and [redacted].

20. [redacted]

21. The capsules are provided in [redacted]

22. These [redacted] respectively, through the inhaler.

23. Defendant's Proposed Label instructs physicians to prescribe Defendant's Proposed Product in [redacted].

24. [redacted] are achieved by instructing patients to inhale the contents of [redacted].

25. [redacted]

26. To achieve a dose that requires [redacted], patients must select their capsules from [redacted]

27. Defendant's Proposed Label describes administration of inhalation [redacted]

28. Defendant's Proposed Product uses "PRINT" particles, which the LIQ861 NDA describes as having an [redacted]

29. The LIQ861 NDA states that [redacted]

30. [redacted]

B. The Yonsung Manufacturing Process

31. In synthetic chemistry, no reaction product is 100% pure.

32. [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

35. [redacted]

36. [redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

69. A drug substance may be used in the commercial manufacture of a drug product despite exposure to temperatures outside the suggested storage temperature range specified in the DMF and/or NDA for that drug substance.

70. [redacted]

73. [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

79. There is no temporal limitation on storage.

C. Administration of Liquidia's Proposed Product

80. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, is to be administered for the treatment of pulmonary arterial hypertension.

81. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, is to be administered to a human suffering from pulmonary hypertension.

82. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, is a dry powder formulation comprising treprostinil sodium, which is a pharmaceutically acceptable salt of treprostinil. The dry powder formulation in Liquidia's Proposed Product includes particles [redacted] The dry

powder formulation in Liquidia's Proposed Product does not contain [redacted]

83. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, is to be administered using the [redacted], which is a dry powder inhaler, which is an inhalation device.

84. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, is to be administered [redacted] Each of those [redacted] is a single event dose. Each of those [redacted] is to be done in [redacted].

85. Liquidia's Proposed Product, as described in its Proposed Label, instructions for use, and in Liquidia's 505(b)(2) Application, includes administration of [redacted] containing [redacted] of treprostinil.

86. The [redacted] of Liquidia's Proposed Product of [redacted] of treprostinil. The [redacted] of treprostinil or a pharmaceutically acceptable salt thereof.

87. Liquidia intends physicians to prescribe, and patients to use, Liquidia's Proposed Product according to the [redacted]

88. Liquidia's Proposed Product is to be stored at [redacted]

D. Defendant's Proposed Product Infringes the '066 Patent

89. The [redacted] unless otherwise specified.

90. [redacted]

[redacted]

92. FDA regulations and other applicable law allow a pharmaceutical company to use a batch of a drug substance in the commercial manufacture of a drug product even though the batch has been exposed to storage temperatures outside of the range established in the DMF and/or NDA, provided there is stability data that supports the use of that material and the company has conducted a proper deviation investigation.

93. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

99. [redacted]

[redacted]

E. Defendant's Proposed Product Infringes the '793 Patent

115. The plain and ordinary meaning of "therapeutically effective" in the claims of the '793 patent is not limited to clinical study endpoints. It includes beneficial effects for the patient, including vasodilatory effects on the pulmonary arteries detectable in hemodynamic measurements, such as those described in the '793 patent.

116. Administration of Liquidia's Proposed Product to patients will meet the claim limitation requiring a "therapeutically effective" single event dose.

117. Administration of Liquidia's Proposed Product by patients will directly infringe claims 1, 4, and 6-8 of the '793 patent.

118. Defendant's Proposed Label and Instructions for Use would encourage, recommend, or promote infringement of claims 1, 4, and 6-8 of the '793 patent by physicians, caregivers, and patients.

119. Based on the contents of its Proposed Label and Instructions for Use, Defendant specifically intends to encourage, recommend, or promote infringement of claims 1, 4, and 6-8 of the '793 patent by physicians, caregivers, and patients.

120. Liquidia will actively induce direct infringement by patients through its press releases, marketing, label, instructions for use, and conduct.

121. Through the sale or offer for sale of Defendant's Proposed Product, Defendant will contribute to the infringement of claims 1, 4, and 6-8 of the '793 patent by patients or physicians or caregivers who administer Defendant's Proposed Product.

122. Defendant has knowledge of the '793 patent at least as early as July 22, 2020; will sell or offer for sale its Proposed Product, which is a product for practicing a patented method, and which is not a staple article or commodity capable of substantial non-infringing use and which constitutes a material part of the invention; and Defendant knows that its Proposed Product was especially made or adapted for use in an infringing method. Thus, Defendant will also contribute to infringement of claims 1, 4, and 6-8 of the '793 patent.

IV. FACTS PERTAINING TO THE VALIDITY OF THE '066, '901, AND '793 PATENTS

A. The '066 and '901 Patents are Valid

123. A POSA would have understood that the '066 and '901 patents satisfy the written description requirement.

124. A POSA would have understood that the inventors were in possession of the "Impurities" limitation of the '066 and '901 patents.

125. A POSA would have understood that the inventors were in possession of the "Salt" limitation of the '066 and '901 patents.

126. A POSA would have understood that the inventors were in possession of the "Stored"/ "Storing"/ "Storage" at "Ambient Temperature" limitations of the '066 and '901 patents.

127. There is no limitation prohibiting column chromatography in the '066 and '901 patents, but nevertheless a POSA would have understood that the inventors were in possession of such a limitation.

128. There is no limitation prohibiting isolation of treprostinil before combining with a base to form a salt in the '066 and '901 patents, but nevertheless a POSA would have understood that the inventors were in possession of such a limitation.

129. A POSA would have understood that the inventors were in possession of the "Therapeutically Effective Amount" limitation of the '901 patent.

130. A POSA would have understood that the '066 and '901 patents satisfy the enablement requirement.

131. A POSA would have been able to practice the "Salt" limitation of the '066 and '901 patents without undue experimentation.

132. A POSA would have been able to practice the "Stored"/ "Storing"/ "Storage" at "Ambient Temperature" limitations of the '066 and '901 patents without undue experimentation.

133. There is no limitation prohibiting column chromatography in the '066 and '901 patents, but nevertheless a POSA would have been able to practice such a limitation without undue experimentation.

134. There is no limitation prohibiting isolation of treprostinil before combining with a base to form a salt in the '066 and '901 patents, but nevertheless a POSA would have been able to

practice such a limitation without undue experimentation.

135. A POSA would have been able to practice the "Therapeutically Effective Amount" limitation of the '901 patent without undue experimentation.

136. A POSA would have understood that the '066 and '901 patents satisfy the definiteness requirement.

137. A POSA would have been able to discern the scope and meaning of the "Impurities" limitation of the '066 and '901 patents with reasonable certainty.

138. A POSA would have been able to discern the scope and meaning of the "Stored"/ "Storing"/ "Storage" at "Ambient Temperature" limitations of the '066 and '901 patents with reasonable certainty.

139. A POSA would have been an experienced chemical engineer or process research chemist with experience in or access to an individual with experience in the production and manufacture of pharmaceutical API and final drug product for pharmaceutical compositions and pharmaceutical products.

140. A POSA would have understood from the '066 and '901 patent specifications that impurities generated during the alkylation step are described in the '066 and '901 patent specifications.

141. A POSA would have understood from the '066 and '901 patent specifications that impurities generated during the hydrolysis step are described in the '066 and '901 patent specifications.

142. Example 1 of each of the '066 and '901 patent specifications describes the alkylation of benzindene triol and provides exemplary reactants and reaction conditions that may be used in that step. A POSA would have understood from Example 1 that impurities would be

generated during the alkylation step.

143. A POSA would have understood that filtering the alkylation product of the ’066 and ’901 patent specifications with Celite pad and washing the filter cake in acetone does not remove all impurities.

144. A POSA would have understood that a light brown color of the benzindene nitrile of the ’066 and ’901 patent specifications indicates the presence of impurities.

145. A POSA would have understood that the ’066 and ’901 patent specifications’ reference to the benzindene nitrile as crude indicates a product that is not in pure form and that contains impurities.

146. Example 2 of the ’066 and ’901 patent specifications describes the hydrolysis of benzindene nitrile and provides exemplary reactants and reaction conditions that may be used in that step. A POSA would have understood from Example 2 that impurities would be generated during the hydrolysis step.

147. A POSA would have understood from the “*Note” in Example 2 of the ’066 and ’901 patent specifications that impurities introduced during the alkylation step are not removed prior to the hydrolysis step.

148. A POSA would have understood from the ’066 and ’901 patent specifications that impurities introduced during the alkylation step that are either carried through or react during the hydrolysis step are impurities resulting from the alkylation and hydrolysis steps.

149. A POSA would have understood from Example 2 in the ’066 and ’901 patent specifications that ethyl acetate extraction does not remove all impurities.

150. A POSA would have understood from Example 2 in the ’066 and ’901 patent specifications that a starting batch of treprostinil, containing impurities resulting from prior

alkylation and hydrolysis steps, was formed prior to the addition of activated carbon.

151. A POSA would have understood from the ’066 and ’901 patent specifications that a pale-yellow color of treprostinil indicates the presence of impurities.

152. A POSA would have understood from the prior art that pure treprostinil is a colorless crystalline solid.

153. A POSA would have understood from Example 2 in the ’066 and ’901 patent specifications that TLC can be used to measure the presence of impurities.

154. A POSA would have understood from the prior art that TLC can be used to measure the presence of impurities.

155. A POSA would have understood from Example 3 in the ’066 and ’901 patent specifications that impurities are present in the treprostinil after the alkylation and hydrolysis steps, for example, from the “*Note” explaining that the treprostinil is not an isolated yield.

156. A POSA would have understood from step 21 in Example 6 in the ’066 and ’901 patent specifications that impurities are present in the hydrolysis product because the step is titled “Removal of impurities.”

157. A POSA would have understood from Example 5 in the ’066 and ’901 patent specifications that the level of one or more impurities were lowered from the starting batch of treprostinil due to the off-white color of the treprostinil after the salt formation step.

158. A POSA would have understood from the ’066 and ’901 patent specifications that the level of one or more impurities is lowered from the starting batch of treprostinil to the pharmaceutical composition from the statement in the specifications that “The impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step.”

159. A POSA would have understood from the prior art how to identify and quantify specific impurities, for example, by using chromatographic techniques. A POSA would also have understood from the prior art how to track the reduction in impurities, even if the identity of the impurities was not known, for example, by correlating impurity peaks at particular retention times.

160. A POSA would have understood from the ’066 and ’901 patents that only bases that will result in the formation of a pharmaceutically acceptable salt can be used during the salt formation step.

161. A POSA would have understood that the ’066 and ’901 patent specifications define the terms “pharmaceutically acceptable,” “pharmaceutically acceptable salts,” and “pharmaceutically acceptable salt.” A POSA would have understood from these definitions which bases could be used to form pharmaceutically acceptable salts.

162. A POSA would have understood from the non-limiting examples in the ’066 and ’901 patent specifications that the following bases could be used during the salt formation step: diethanolamine, ammonia, N-methylglucamine, procaine, tromethamine, magnesium, L-lysine, L-arginine, and triethanolamine.

163. A POSA would have understood from claim 3 of the ’066 patent that the following bases could be used during the salt formation step: sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

164. There is no temporal limitation on storage.

165. Storage can occur between manufacturing steps and during transportation.

166. A POSA would have understood from Example 3 in the ’066 and ’901 patent specifications that treprostinil salt is formed once the seed of polymorph B of treprostinil diethanolamine was added.

167. A POSA would have understood from Example 3 in the ’066 and ’901 patent specifications that treprostinil salt is stored at ambient temperature when the suspension was cooled to 20 ± 2° C overnight.

168. A POSA would have understood from Example 3 in the ’066 and ’901 patent specifications that treprostinil salt is stored at ambient temperature when the treprostinil diethanolamine salt was transferred to a container for air drying in hood.

169. A POSA would have understood from Example 4 in the ’066 and ’901 patent specifications that isolated salt is stored at ambient temperature when it was transferred to trays for air-drying overnight in hood.

170. A POSA would have understood from steps 32 and 34 of Example 6 in the ’066 and ’901 patent specifications that isolated salt is stored at ambient temperature.

171. A POSA would have understood from the ’066 and ’901 patent specifications that isolated salt and treprostinil salt could be stored at ambient temperature where it states “crude treprostinil salts can be stored as raw material at ambient temperature.”

172. A POSA would have understood from the prior art how to control for non-temperature storage conditions such as humidity, light, and oxygen levels.

173. A POSA would have understood that prohibition of column chromatography is not claimed in the ’066 and ’901 patents.

174. Claims 1 and 8 of the ’066 patent and claim 8 of the ’901 patent are comprising claims such that steps in addition to those claimed could be present and still be within the scope of the claim.

175. A POSA would have understood from the ’066 and ’901 patent specifications that the inventors were showing a preferred embodiment whereby column chromatography could be

eliminated, rather than a disclaimer or disavowal of the use of column chromatography.

176. A POSA would have understood that the ’066 and ’901 patents define “comprising” as “including but not limited to” such that “other non-mentioned…steps may be present.”

177. A POSA would have understood from step 12 of Example 6 of the ’066 and ’901 patent specifications that column chromatography could be practiced between the alkylation and salt formation steps.

178. A POSA would have understood from the prior art that column chromatography was a routine and well-known purification technique.

179. A POSA would have understood from the ’066 and ’901 patent specifications that there can be isolation prior to salt formation.

180. A POSA would have understood from the ’066 and ’901 patent specifications that various other purification techniques besides column chromatography could be used between alkylation and salt formation such as Celite pad filtering, ethyl acetate extraction, NaCl washing, carbon filtration, and ethyl acetate washing.

181. A POSA would have understood from the prior art that column chromatography does not always result in a more pure product.

182. A POSA would have understood that prohibition of isolation of treprostinil before combining with a base is not claimed in the ’066 and ’901 patents.

183. A POSA would have understood from the ’066 and ’901 patent specifications that the inventors were showing a preferred embodiment whereby of isolation of treprostinil before combining with a base could be eliminated, rather than a disclaimer or disavowal of isolation of treprostinil before combining with a base.

184. A POSA would have understood from Example 2 in the ’066 and ’901 patent

specifications that the volume of a solution of treprostinil was reduced prior to combination with a base. A POSA would have understood from this disclosure that the treprostinil could have been isolated by continuing to reduce the volume of the filtrate.

185. A POSA would have understood from the ’066 and ’901 patent specifications that treprostinil was an FDA approved medication and would have been able to determine a therapeutically effective amount of treprostinil or salt thereof based on the numerous references described in the specification.

186. A POSA would have understood from the ’066 and ’901 patent specifications that treprostinil is the active ingredient in Remodulin®.

187. A POSA would have understood from the prior art, for example the March 2006 Remodulin® label, information on disease, dosing, and route of administration.

188. As to the ’066 and ’901 patents, the critical date for availability as prior art is December 17, 2007.

189. U.S. Patent No. 8,497,393 (“the ’393 patent”) issued July 30, 2013, resulting from U.S. Patent Application Number 13/548,446, which is a continuation of U.S. Patent Application No. 12/334,731, filed on December 15, 2008, now U.S. Patent No. 8,242,305. The ’393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232, the same provisional application to which the ’066 and ’901 patents claim priority.

190. The ’066 and ’901 patent specifications at 1:8-15 cite and incorporate by reference the application of the ’393 patent.

191. The ’393 patent is not prior art to the ’066 patent.

192. The ’393 patent is not prior art to the ’901 patent.

193. The ’066 patent claims contain limitations not found in the ’393 patent claims.

194. The ’901 patent claims contain limitations not found in the ’393 patent claims.

195. Claim 1 of the ’393 patent is a genus claim.

196. Claim 1 of the ’393 patent does not contain a limitation on impurities.

197. Claim 1 of the ’393 patent does not contain a limitation on stability.

198. The ’066 and ’901 patent specifications at 1:27-34 cite and incorporate by reference the paper “Moriarty, *et al* in J. Org. Chem. 2004, 69, 1890-1902” (“Moriarty”).

199. During prosecution of the ’066 patent, the examiner considered the reference WO 2005/007081 (“Phares”) listed on page 2 of the ’066 patent under references cited.

200. During prosecution of the ’901 patent, the examiner considered the reference WO 2005/007081 (“Phares") listed on page 2 of the ’901 patent under references cited.

201. The ’066 and ’901 patents do not claim the same product as in the prior art.

202. The pharmaceutical compositions and batches claimed in the ’066 and ’901 patents are distinct from products in the prior art.

203. The ’066 and ’901 patents have claims directed towards making pharmaceutical compositions and pharmaceutical products that are different from methods found in the prior art.

204. The storage of isolated treprostinil salt at ambient temperature during manufacture of a pharmaceutical composition is claimed in the ’066 and ’901 patents and is not disclosed in the prior art.

205. Prior art does not render obvious claim 1 of the ’066 patent.

206. The prior art does not disclose the lowering of impurities from a starting batch of treprostinil.

207. The prior art does not disclose the impurities present in the product of Moriarty.

208. Prior art does not render obvious claim 2 of the ’066 patent

209. Prior art does not render obvious claim 3 of the ’066 patent.

210. Prior art does not render obvious claim 6 of the ’066 patent.

211. The prior art does not disclose storing an isolated salt of treprostinil at ambient temperature.

212. Prior art does not render obvious claim 8 of the ’066 patent.

213. Prior art does not render obvious claim 9 of the ’066 patent.

214. Prior art does not render obvious claim 1 of the ’901 patent.

215. Prior art does not render obvious claim 2 of the ’901 patent.

216. Prior art does not render obvious claim 3 of the ’901 patent.

217. Prior art does not render obvious claim 4 of the ’901 patent.

218. Prior art does not render obvious claim 6 of the ’901 patent.

219. Prior art does not render obvious claim 8 of the ’901 patent.

220. Prior art does not render obvious claim 9 of the ’901 patent.

221. UTC release specifications and other FDA submissions do not show that the claimed compositions were in the prior art.

222. UTC release specifications do not affect the scope of the ’066 patent.

223. UTC release specifications do not affect the validity of the ’066 patent.

224. UTC release specifications do not affect the scope of the ’901 patent.

225. UTC release specifications do not affect the validity of the ’901 patent.

226. FDA submissions do not impact the scope of the ’066 patent.

227. FDA submissions do not impact the validity of the ’066 patent.

228. FDA submissions do not impact the scope of the ’901 patent.

229. FDA submissions do not impact the validity of the ’901 patent.

230. A POSA would not have been motivated to combine Moriarty and Phares with a reasonable expectation of success.

231. A POSA would not have been motivated to combine Moriarty and Phares.

232. Phares does not disclose the stability of any polymorphic form of treprostinil diethanolamine at ambient temperature.

233. A POSA would understand that more thermodynamic stability does not equate to stability at room temperature.

234. A POSA would not be motivated to combine Phares based on the bioavailability disclosed in Phares.

235. The pharmaceutical composition of the ’066 patent is structurally and functionally different from products of the prior art.

236. The pharmaceutical batch of the ’901 patent is structurally and functionally different from products of the prior art.

237. In issuing the ’066 patent, the examiner considered Moriarty and Phares and found the claims nonobvious over the combination.

238. Liquidia petitioned for *inter partes* review (IPR) of the ’066 patent, arguing obviousness in the combination of Moriarty and Phares. The PTAB denied institution of IPR for the ’066 patent.

239. Liquidia petitioned for IPR of the ’901 patent, arguing Moriarty and Phares obviousness in the combination of Moriarty and Phares.

240. The PTAB instituted review of the ’901 patent based on Liquidia’s petition.

241. The PTAB issued a Final Written Decision on the ’901 patent.

242. Liquidia is estopped under § 315 from arguing invalidity based on grounds it raised

or reasonably could have raised in the ’901 IPR.

243. In issuing the ’901 patent, the examiner considered Moriarty and Phares and found the claims nonobvious over the combination.

244. Tyvaso practices the claimed invention.

245. Tyvaso is a commercial success.

246. A POSA would not know UTC confidential information in considering motivation to combine prior art.

247. [redacted]

[redacted] [redacted]

249. A POSA would not know UTC confidential information in considering the disclosure of prior art.

250. A POSA would not use the invention as a roadmap in looking at the prior art.

251. There is no evidence of a motivation to combine the teachings of the prior art other than using hindsight of the invention as a roadmap.

252. A POSA would not have a reasonable expectation of success in scaling up the prior art processes.

253. A POSA would understand the prior art did not teach commercial scale manufacturing of treprostinil.

254. A POSA would understand that laboratory scale experiments are not always able to be scaled to commercial scale.

255. The prior art does not disclose any problems with the white-needle crystalline

appearance of treprostinil.

256. A POSA would not consider white-needles to be an issue from the prior art.

257. [redacted]

258. A POSA would know that statements in the prior art of quality and safety made to the FDA do not affect the scope of the ’066 patent.

259. A POSA would know that statements in the prior art of quality and safety made to the FDA do not affect the validity of the ’066 patent.

260. A POSA would know that statements in the prior art of quality and safety made to the FDA do not affect the scope of the ’901 patent.

261. A POSA would know that statements in the prior art of quality and safety made to the FDA do not affect the validity of the ’901 patent.

262. The diethanolamine salt disclosed in the ’066 is not identical to the diethanolamine salt in Phares.

263. The diethanolamine salt disclosed in the ’901 is not identical to the diethanolamine salt in Phares.

B. The Claims of the ’793 Patent are Valid

1. The ’793 Patent

264. The ’793 patent, filed on January 31, 2020, is entitled “Treprostinil Administration by Inhalation,” and was issued on July 21, 2020. The ’793 Patent is directed to the treatment of pulmonary hypertension by administering treprostinil (or salts thereof) by inhalation.

265. The ’793 patent was granted on application number 16/778,662, filed January 31, 2020, and claims priority through a series of applications dating back to a provisional patent

application, 60/800/016, filed on May 15, 2006. The priority date for the ’793 patent is not later than May 15, 2006.

266. The named inventors of the ’793 patent are Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt and Robert Voswinckel.

267. The ’793 patent relates to a therapy involving treatment of pulmonary hypertension using inhaled treprostinil. Specifically, the ’793 patent relates to a method of treating pulmonary hypertension by administering an inhaled, therapeutically effective, single event dose that comprises from 15 to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof, delivered in 1 to 3 breaths.

268. The ’793 patent claims several inhalation devices for administration, including administration using a dry powder inhaler. The ’793 patent also claims a formulation including treprostinil, or a pharmaceutically acceptable salt thereof, wherein the formulation is a dry powder formulation.

269. UTC has asserted that Liquidia infringes five claims of the ’793 patent: Claims 1, 4, 6, 7 and 8 of the ’793 patent.

270. Claims 4, 6, 7 and 8 depend from Claim 1 of the ’793 patent.

2. Person of Ordinary Skill in the Art

271. The named inventors of the ’793 patent have post-graduate degrees in the field of medicine or drug development disciplines and all had at least several years of research, executive, and/or clinical experience in the investigation and treatment of pulmonary hypertension and in developing pharmaceutical products for the treatment of pulmonary hypertension.

272. A POSA with respect to the ’793 patent would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or a Ph.D., with at least two years practical

experience in either (i) the investigation or treatment of pulmonary hypertension or (ii) in the development of potential drug candidates, specifically in the delivery of drugs by inhalation.

273. The POSA could have a lower level of formal education if such a person had more years of experience in the development of inhalable drugs.

274. Because drug development involves a multidisciplinary approach, the POSA would consult with individuals having specialized expertise, for example, a pharmacologist with experience in development of inhaled formulations or inhalation devices and/or a physician with experience in the administration, dosing and efficacy of drugs for the treatment of a particular disease state.

3. Relevant Claim Construction

275. The Court did not construe any terms or phrases in the ’793 patent and as such, the terms should have their plain and ordinary meaning to the POSA .

4. Relevant Background

276. Pulmonary hypertension is a term for a hemodynamic abnormality, elevated pressure. For pulmonary hypertension, a hemodynamic effect is a therapeutic effect showing improvement on the underlying state of the disease. Administration of a drug like treprostinil that has a vasodilatory effect on pulmonary arteries and reduces pressure (e.g., PAP) and pulmonary resistance (e.g., PVR) directly addresses the elevated pressure associated with pulmonary hypertension. This reduction in the pressure load on the heart is a therapeutic effect that is demonstrated by the data presented in the ’793 patent specification.

277. Hemodynamics can be and are used to assess efficacy of drugs, including in clinical studies and drug development. The benefit of hemodynamics when assessing therapeutic effectiveness against pulmonary hypertension is clear from numerous clinical studies gathering

hemodynamic data to determine test effectiveness.

278. The first FDA approved treatment for pulmonary hypertension – and the sole approved treatment for over five years (from 1995-2001) – was epoprostenol, which had substantial shortcomings and posed significant burdens to patients.

279. Epoprostenol can only be administered by continuous intravenous infusion because it has a short half-life of only a few minutes and is cleared from the body very quickly. Further, the short duration of action of epoprostenol means that even a brief interruption in infusion could increase the risk of hemodynamic collapse and even death because of delivery complications. Moreover, epoprostenol requires daily mixing and refrigeration, thus requiring the patient to carry a cold pack to avoid degradation at room temperature and an infusion pump in order to safely administer the drug.

280. Later-approved subcutaneous (in 2002) and intravenous (in 2004) administration of treprostinil had some benefits over epoprostenol. For example, it is stable at room temperature and has a half-life of several hours rather than several minutes. This freed patients of having to carry ice packs to ensure the safety and efficacy of the drug. There were still limitations to intravenous and subcutaneous delivery of treprostinil, such as intolerable site pain in some instances and systemic side effects.

281. By the May 2006 priority date of the ’793 patent, the only FDA-approved prostacyclin-type drug that could be given in an inhalable form was iloprost, marketed as Ventavis®. Clinicians were still largely of the opinion however, that intravenous administration of a prostacyclin analog was preferable to inhaled delivery of iloprost for a number of reasons, including iloprost’s relatively short half-life.

282. By May 2006, a large number and variety of devices suitable for use with powder

formulations were known.

283. Specifically, one such company in Italy known as Plastiape made devices (e.g., dry powder inhalers) that were known, available, and used widely in the market with many milled and/or spray-dried powders.

284. At the time of the priority date, the basic principles of dry powder formulation development were known and available. The basic steps in formulating dry powder formulations of drugs were known and studied by 2006. Known techniques included micronization and spray drying, as well as ways to evaluate, modify process steps, and improve or optimize processes to achieve respirable particle sizes. It was known to test and evaluate formulations and devices using in vitro methods, including, among others, impaction studies. Further optimization regarding formulation, drug and carrier to reach a desired performance was known and routine at the time of the priority date.

285. At the time of the priority date, the basic principles of dry powder formulation development were known and available. Information regarding the active pharmaceutical ingredient, preparation of the active pharmaceutical ingredient, use of excipients and formulations for dry powder inhalers, how formulations are processed, and techniques used to characterize dry powder formulation systems was readily available.

286. Information regarding drug properties, milling, excipient selection, blending, and filling into a dry powder inhaler device was similarly known and available. Furthermore, guides concerning dry powder inhaler devices and knowledge regarding the accuracy and reproducibility of dose emissions from those devices was available.

287. Salt synthesis for APIs, physical and chemical screening, XRPD, laser diffraction, cascade impaction, HPLC, blending, mixing, blend uniformity, and many other techniques, were

known as part of the drug development and formulation evaluation and improvement processes.

5. Prior Art

a) The ’212 Patent

288. The ’212 patent describes testing done in tracheotomized sheep, involving UT-15 delivered by inhalation using a continuous nebulizer.

289. The ’212 patent is listed on the face of the ’793 patent under “References Cited,” and was considered by the patent examiner before the ’793 patent was allowed.

290. The ’212 patent does not disclose a dose to be administered to sheep or humans in a single event.

291. The ’212 patent does not contain sufficient information to allow a POSA to calculate a therapeutically effective single event dose of 15-90 μg delivered in 1-3 breaths from the information given in the abstract, let alone to do so reliably, for a sheep or human.

292. The ’212 patent does not disclose, teach, or render obvious the administration of inhaled treprostinil to a human in 1-3 breaths.

293. The ’212 patent does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’793 patent.

b) Voswinckel JESC

294. Voswinckel JESC is a brief abstract spanning approximately one quarter of a single page that generally describes a clinical study that used continuous nebulization at concentrations of 16, 32, 48, and 64 μg/mL of treprostinil with a time period of 6 minutes.

295. Voswinckel JESC provides the concentration of the drug in the pre-aerosolized solution but does not specify the dose delivered to the patient. Voswinckel JESC does not describe a therapeutically effective single event dose of 15 micrograms to 90 micrograms.

296. Voswinckel JESC does not contain sufficient information to allow a POSA to calculate a therapeutically effective single event dose of 15-90 µg delivered in 1-3 breaths from the information given in the abstract, let alone to do so reliably.

297. In general, a POSA would not rely on an abstract like Voswinckel JESC because conference abstracts are not peer-reviewed to the same rigor as published journal articles, and further often report only preliminary data which may or may not translate into actual results.

298. Voswinckel JESC is listed on the face of the ’793 patent under “References Cited,” and was thus considered by the patent examiner before the ’793 patent was allowed.

299. Voswinckel JESC does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’793 patent.

c) Voswinckel JAHA

300. Voswinckel JAHA is a brief abstract spanning approximately one quarter of a single page in the Circulation Journal of the American Heart Association. It generally describes preliminary data of an open-label study of “TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml).” This abstract discloses a pre-aerosolized concentration for the treprostinil solution of 600 µg/mL for inhalation over a specific number of breaths. Voswinckel JAHA also does not describe a therapeutically effective single event dose of 15 micrograms to 90 micrograms.

301. Voswinckel JAHA does not contain sufficient information to allow a POSA to calculate a therapeutically effective single event dose of 15-90 µg delivered in 1-3 breaths from the information given in the abstract, let alone to do so reliably.

302. In general, a POSA would not rely on an abstract like Voswinckel JAHA because conference abstracts are not peer-reviewed to the same rigor as published journal articles, and

further often report only preliminary data which may or may not translate into actual results.

303. Voswinckel JAHA is listed on the face of the ’793 patent under “References Cited,” and was considered by the patent examiner before the ’793 patent was allowed.

304. Voswinckel JAHA does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’793 patent.

d) Ghofrani

305. Ghofrani is a review article, published in German, describing “New therapies in the treatment of pulmonary hypertension.” In addition to describing recent developments relating to inhaled treprostinil, the review article also describes other “new therapy approaches, which are partially still under development, and that can find their way into the therapy guidelines in the near future” including inhaled iloprost, selective endothelin A receptor antagonists (sitaxsentan and ambrisentan), and PDE-5 inhibitors.

306. Ghofrani was co-authored by Dr. Werner Seeger and Dr. Robert Voswinckel (inventors of the ’793 patent) as well as Dr. Hossein A. Ghofrani, Dr. Frank Reichenberger, and Dr. Friedrich Grimminger. Ghofrani was published in June of 2005.

307. The work described in Ghofrani and relied upon by Liquidia is not “by another.”

308. Ghofrani does not qualify as prior art.

309. Ghofrani is listed on the face of the ’793 patent under “References Cited,” and was considered by the patent examiner before the ’793 patent was allowed.

310. Ghofrani does not alone, or in combination with Liquidia’s other asserted prior art, anticipate or render obvious any claims of the ’793 patent.

e) Voswinckel 2006

311. Voswinckel 2006 is a short “Clinical Observation” published in the Annals of

Internal Medicine, titled "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," which describes clinical observations on three patients with severe pulmonary hypertension, who were treated with administration of a single 15 μg dose of treprostinil, inhaled in three breaths through a modified Optineb ultrasonic inhalation device.

312. Voswinckel 2006 was co-authored by Dr. Werner Seeger, Dr. Robert Voswinckel, and Dr. Horst Olschewski (inventors of the '793 patent) as well as Dr. Hossein A. Ghofrani and Dr. Friedrich Grimminger. Voswinckel 2006 was published in January of 2006.

313. The work described in Voswinckel 2006 and relied upon by Liquidia is not "by another."

314. Voswinckel 2006 does not qualify as prior art.

315. Voswinckel 2006 is listed on the face of the '793 patent under "References Cited," and was considered by the patent examiner before the '793 patent was allowed.

316. Voswinckel 2006 does not alone, or in combination with Liquidia's other asserted prior art, anticipate or render obvious any claims of the '793 patent.

6. Secondary Considerations

317. Tyvaso is a commercial embodiment of the '793 patent. Tyvaso is used to treat pulmonary hypertension in humans suffering from pulmonary hypertension and is administered in a therapeutically effective single event dose comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, and the therapeutically effective single event dose is between 15 to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof and is delivered in 1 to 3 breaths.

318. The '793 patent satisfied a long-felt but unmet need.

319. The '793 patent allowed for an inhaled dosing regimen and maximized therapeutic

benefits by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy to use inhaler.

320. Inhaled treprostinil is approved to treat a broader range of pulmonary hypertension patients than the therapeutics available at the time of the invention.

321. The ’793 patent showed unexpected results including that therapeutically effective, high doses of treprostinil could be delivered to a patient in a shorter period of time with fewer side effects be developing a method that combined higher dosing in fewer breaths using a modified inhalation device.

322. The pharmacodynamics of inhaled treprostinil also presented unexpected results.

323. Tyvaso is currently approved in the U.S. for the treatment of PAH and PH-ILD.

7. The Asserted Claims of the ’793 Patent Are Enabled And Have Adequate Written Description

324. The ’793 patent satisfies the written description and enablement requirements.

325. The ’793 patent discloses both an inhalable solution and an inhalable dry powder and devices for administering both types of formulations.

326. The ’793 patent provides for both a dry powder with a particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter as well as an inhalation device that can be a dry powder inhaler.

327. The ’793 patent describes treprostinil dosing information, the use of dry powder inhalers, and powder formulations.

328. The POSA would recognize based on the ’793 patent that the inventors were in possession of, i.e., had invented what is claimed, an inhaled dry powder formulation of treprostinil.

329. The ’793 patent contains adequate written description supporting the asserted claims, including the claims including methods of treatment using dry powder formulations and/or

dry powder inhalers.

330. A POSA in 2006 would have had access to numerous dry powder inhalers (DPIs), excipients, and methods of manufacturing dry powder formulations.

331. Numerous devices existed by 2006 that would have been suitable for use with inhaled dry powder formulations.

332. A sufficient number of carriers existed in 2006 that a POSA could have chosen from, including lactose.

333. Methods were also known to a POSA as of the priority date that would allow a POSA to adjust API and excipient particle size to achieve the desired particle sizes and formulation performance.

334. Starting with the information disclosed in the ’793 patent, a POSA could have used known excipient(s) and known techniques such as milling or spray drying to create an inhalable dry powder formulation of treprostinil (or a salt thereof) and practice the asserted claims of the ’793 patent without undue experimentation.

335. The experimentation required to prepare an inhalable dry powder formulation of treprostinil (or a salt thereof) for use in a dry powder inhaler (DPI) and practicing the asserted claims of the ’793 was routine and would not be considered undue.

336. In 2006, a POSA reviewing the claim limitation requiring a method of treating pulmonary hypertension would immediately understand that the claim was referring to pulmonary arterial hypertension.

337. To the extent the claim is interpreted to cover all forms of pulmonary hypertension, a POSA would have understood that as of the priority date inhaled treprostinil could be used to treat multiple forms of pulmonary hypertension, including based upon the ’793 patent

specification.

338. A POSA would have understood that the ’793 patent includes WHO Groups 1, 3, and 4 within the patent specification, that WHO Group 5 could also be included, and that inhaled treprostinil could be used to treat a mixed form of WHO Group 2.

339. As of the priority date a POSA would have known and understood that inhaled treprostinil would not be used to treat a pure WHO Group 2 post-capillary patient.

340. The POSA could readily determine from his or her knowledge and skill, or from routine testing, whether inhaled treprostinil could be used to treat WHO Group 2 postcapillary PH.

341. The POSA would recognize based on the ’793 patent that the inventors were in possession of, i.e., had invented what is claimed, a method of treating pulmonary hypertension.

342. The POSA would have been able to practice the claimed methods of treating pulmonary hypertension without undue experimentation based on the teachings of the ’793 patent and the background knowledge of those of skill in the art.

343. The POSA could have practiced the asserted claims of the ’793 patent—i.e., could have administered a formulation (e.g., a liquid or dry powder) to a human consistent with the claims—without undue experimentation. The POSA knew how to prepare and administer formulations and would have been able to instruct the patient on how to use the formulations to administer the drug using routine techniques and without undue experimentation.

EXHIBIT 12

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 20-755 (RGA) (JLH) **HIGHLY CONFIDENTIAL**

<u>REBUTTAL EXPERT REPORT OF ANDREW CLARK, PH.D.</u>

TABLE OF CONTENTS

I. INTRODUCTION

A. Scope of Analysis

1. I have been retained by counsel for the Plaintiff, United Therapeutics Corporation ("UTC") to provide expert opinions related to U.S. Patent No. 10,716,793 ("the '793 patent").

2. I am being compensated for my time spent on this matter at the rate of $400 per hour, plus reasonable expenses. I have no other interest in this litigation or in any party to this litigation. My compensation does not depend on my performance, the substance of my opinions, the outcome of the case, or any issues involved in or related to this case.

B. Qualifications

3. My *curriculum vitae*, which is attached as **Exhibit 1**, summarizes my professional experience. I provide below further details about my experience that may be pertinent to this matter.

4. I provided my background and qualifications in paragraphs 9–18 of my Initial Expert Report. I hereby incorporate by reference that background information.

C. Materials Considered

5. In forming the opinions described in this report, I have relied on my professional experience and personal knowledge. I have also reviewed a number of documents and materials in this case. A full list of the materials considered, in whole or in part, in forming my opinions is set forth in **Exhibit 2**, attached hereto.

6. My analysis of the issues of validity discussed in this report and my rebuttal to assertions made by Dr. Hill and/or Dr. Gonda has taken into account the Court's Construction of the Asserted Claims as set forth in the Court's June 16, 2021, Claim Construction Order (D.I. 119), which I have reviewed in full, and the hearing transcript from the Claim Construction Hearing, which I have reviewed in relevant part. If any claim terms were construed or addressed by the

> Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.

Id. at (57); *see also*, *id.* at 7:13-15 (describing a metered dose inhaler as a "device capable of delivering a metered or bolus dose of respiratory drug, such as treprostinil, to the lungs.").

34. The '793 patent relates to a therapy involving treatment of pulmonary hypertension using inhaled treprostinil. Specifically, the '793 patent relates to a method of treating pulmonary hypertension by administering an inhaled, therapeutically effective, single event dose that comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof, delivered in 1 to 3 breaths. *See, e.g.*, '793 patent, claim 1. I understand that the '793 patent claims several inhalation devices for administration, including administration using a dry powder inhaler. I further understand the '793 patent claims a formulation including treprostinil, or a pharmaceutically acceptable salt thereof, wherein the formulation is a dry powder formulation.

35. I understand that the '793 patent was granted on application number 16/778,662, filed January 31, 2020. *Id.* at (21), (22). The '793 claims priority through several other applications, as described under the "Related U.S. Application Data" heading on the cover of the patent. According to the '793 patent, the earliest application filed is provisional application 60/800,016, filed on May 15, 2006. I understand this to be the relevant date—the "priority date"—from which the level of ordinary skill of the POSA is to be determined and the obviousness, written description, and enablement analyses are to be assessed.

C. File History

36. As mentioned, U.S. patent application number 16/778,662 was filed on January 31, 2020. *See, e.g.*, U.S. Patent No. 10,716,793 File History ("'793 File History") (UTC_LIQ00007134-UTC_LIQ00007341) at UTC_LIQ00007137. On May 15, 2020, I

of the priority date, the POSA would understand that the inventors possessed the claimed invention.

46. Claim 1 recites a method of treating pulmonary hypertension through administration of treprostinil, or a pharmaceutically acceptable salt, by inhalation 15-90 μg delivered in 1-3 breaths. The specification of the ’793 patent as 12 pages of figures and 9 pages of narrative description, including two examples showing example devices and resulting data therefrom. Example 1 shows doses of 30-60 μg delivered in 1-3 breaths, resulting in the effective amount of treprostinil can be delivered in a single breath and was well tolerated at higher doses. Example 1 also showed a high concentration treprostinil solution delivered by soft mist inhaler. Example 2 showed doses of 15-90 μg delivered in 1-3 breaths delivered by a pulsed ultrasonic nebulizer. The results showed high doses delivered in minimal inhalation time lead to long-lasting pulmonary vasodilation.

47. Dr. Gonda nevertheless contends that the ’793 patent does not disclose enough about powder formulations and DPIs. In my opinion, he is incorrect. As he acknowledges, the ’793 patent describes treprostinil dosing information (Gonda Report, ¶54) and the use of DPIs and describes powder formulations. ’793 Patent 7:22-26 (discussing powder 5 or 10 micrometers in diameter for use in DPI), 9:14-17 (discussing doses of 30, 45, and 60 μg), 17:42-18:5 (describing doses of 15 μg up to 90 μg), 18:23-31. I also note that the provisional application to which the ’793 patent claims priority, filed May 15, 2006, also describes powder formulations and DPIs. ’016 Provisional at ¶[0036] (“The inhalation device can also be a dry powder. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.”); *id.* at 27 (reciting,

EXHIBIT 13

LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

700 THIRTEENTH STREET, N.W.

SUITE 1200

WASHINGTON, D.C. 20005-5929

(202) 737-5600

FACSIMILE
(202) 737-9329

www.hpm.com

KURT R. KARST
MICHAEL D. SHUMSKY
SARA W. KOBLITZ

Direct Dial (202) 737-7544

February 12, 2024

SUBMITTED BY EMAIL

CONFIDENTIAL TREATMENT REQUESTED PER 21 C.F.R. § 20.61

Kim Dettelbach, Esq.
Assistant Deputy Chief Counsel
Office of the Chief Counsel
U.S. Food and Drug Administration
10903 New Hampshire Avenue
White Oak Building 1
Silver Spring, Maryland 20993-0002

Email: Kim.Dettelbach@fda.hhs.gov

Brian Cooney, MS, PSM
Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for
Cardiology, Hematology,
Endocrinology, & Nephrology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Email: brian.cooney@fda.hhs.gov

Re: NDA 213005 – YUTREPIA (Treprostinil) Inhalation Powder
Response to February 2, 2024 Letter from Liquidia Technologies, Inc.

Dear Ms. Dettelbach and Mr. Cooney:

On behalf of our client, United Therapeutics Corporation ("UTC"), we write in response to the letter dated February 2, 2024 from Liquidia Technologies, Inc. ("Liquidia") pertaining to its pending New Drug Application ("NDA") 213005 ("the YUTREPIA 505(b)(2) NDA") submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and referencing UTC's TYVASO® (treprostinil) inhalation powder approved under NDA 022387. Ltr. from S. Lassman re Liquidia (Feb. 2, 2024) ("Liquidia Ltr.").

As UTC's December 29, 2023 letter explained, the U.S. Food and Drug Administration ("FDA" or "the Agency") erred in accepting Liquidia's attempt to amend its pending 505(b)(2) NDA because that course of action is foreclosed by FDA's

longstanding, consistently applied, and never-previously-challenged Bundling Rule. Ltr. from K. Karst re Liquidia (Dec. 29, 2023) ("UTC Ltr."). Accordingly, the UTC Letter requested that FDA comply with its Bundling Rule and past precedents by withdrawing—or directing Liquidia to withdraw—the YUTREPIA 505(b)(2) NDA amendment and requiring a new NDA submission.

Liquidia's letter provides no persuasive reason why this request should not be granted. Although it claims that the Bundling Rule is outdated and was superseded by rulemaking, the very same rulemaking materials cited in the Liquidia Letter expressly provide that FDA's Bundling Rule remains in full force and effect. Indeed, while the Liquidia Letter paints a picture of a new regulatory scheme permitting the addition of new indications to pending NDAs by way of amendment, that "new" regulatory scheme makes clear that the Bundling Rule remains very much in effect. With its convoluted explanation of FDA's Medicare Modernization Act of 2003 ("MMA") rulemakings, Liquidia encourages FDA to ignore more than 30 years of clear policy—policy directly cited in the very preambles enacting the rulemaking Liquidia relies upon—in a blatant attempt to circumvent both FDA's longstanding Bundling Rule and the 30-month stay provisions Congress enacted in order to provide for an orderly resolution of patent disputes prior to the approval of pending 505(b)(2) NDAs and Abbreviated New Drug Applications ("ANDAs").

Given the misleading nature of the Liquidia Letter and the continued relevance of the Bundling Rule, UTC reiterates that Liquidia wrongly submitted, and that FDA erred in accepting, Liquidia's amendment adding a new indication to its YUTREPIA 505(b)(2) NDA. For that reason, UTC continues to request that FDA require Liquidia to submit a new 505(b)(2) NDA to request approval of a new indication; certify to the patent information listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") as of the submission of that new NDA for any listed drug relied on for approval; and stay the approval of any new YUTREPIA 505(b)(2) NDA if there is timely filed patent infringement litigation in response to a notice of Paragraph IV certification to Orange Book-listed patent information.

I. BACKGROUND

A. Legal Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act" or "Hatch-Waxman"), Pub. L. No. 98-417, 98 Stat. 1585, amended the FDC Act to remove barriers to entry, increase availability of drugs, and reduce prescription

costs. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998). In so doing, the Hatch-Waxman Act established an abbreviated pathway to market for drug products, including both duplicates and follow-on products, by allowing applicants to rely on FDA's findings of safety and effectiveness for other drug products—"listed drugs"—as the basis of approval. 21 U.S.C. § 355(j), (b)(2). Applicants submit either an ANDA or a 505(b)(2) NDA referencing a drug listed in the Orange Book with data "bridging" the proposed drug to the listed drug so that the applicant need not duplicate the extensive testing performed by the listed drug sponsor for approval. *Id.* This process allows more affordable drugs to come to market more quickly than if full studies for safety and effectiveness were required.

At the same time, however, the Hatch-Waxman Act recognized that many listed drugs are protected by valuable patents, and thus struck a balance between expediting follow-on product entry and respecting innovators' patent rights. To that end, Hatch-Waxman requires an NDA sponsor to file with FDA "the patent number and the expiration date of any patent which claims the drug . . . and with respect to which a claim of patent infringement could reasonably be asserted [against a competitor]," 21 U.S.C. § 355(b)(1); *see also* 21 C.F.R. § 314.50(h), and obligates FDA to "publish" and "make available to the public" a list of the patent data NDA holders have submitted to the Agency. 21 U.S.C. § 355(j)(7)(A)(i); *see also id.* § 355(c)(2). FDA publishes this patent information in the Orange Book. *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004).

To speed the resolution of patent disputes between brands and follow-on sponsors so that competition can start as soon as the law permits, Congress required each ANDA or 505(b)(2) NDA relying on a listed drug to include "a certification . . . with respect to each [Orange Book-listed] patent which claims the listed drug . . . or . . . a use for such listed drug." 21 U.S.C. § 355(j)(2)(A)(vii); *see also* 21 C.F.R. § 314.53(f). Several patent certification types are available. *See* 21 U.S.C. § 355(j)(2)(A)(vii).

Paragraph IV certifications are particularly integral to the statutory and regulatory scheme. To help follow-on sponsors obtain certainty about a listed patent's coverage without subjecting them to the *in terrorem* threat of massive damages, the Patent Act deemed an applicant's submission of a Paragraph IV certification to FDA to be a "highly artificial" act of patent infringement that immediately can be litigated without subjecting the follow-on applicant to damages. 35 U.S.C. § 271(e); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990) ("Quite obviously, the purpose of [35 U.S.C. § 271](e)(2) and (e)(4) is to enable the judicial adjudication upon which the ANDA and paper NDA schemes depend."). Where an applicant submits a Paragraph IV certification in its original 505(b)(2) NDA, such notice must be provided "not later than 20 days after the date … [on]

which [FDA] informs the applicant that the application has been filed. *Id.* § 355(b)(3)(B)(i).

Because the whole point of Hatch-Waxman's patent-submission, patent-listing, Paragraph IV certification, and Paragraph IV notice provisions is to resolve patent disputes before FDA approval, the statute incentivizes brand manufacturers to sue as soon as they receive the legally-required notice. When the brand manufacturer sues within 45 days of receiving the legally-required notice, FDA may not approve the follow-on application until 30 months after the brand manufacturer receives the legally-required notice. 21 U.S.C. § 355(c)(3)(C). This 30-month stay permits the innovator and follow-on manufacturer to litigate all relevant patents prior to approval and market entry of the follow-on product. *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 557 F.3d 1346, 1348-49 (Fed. Cir. 2009). A 30-month stay is available only with respect to patent information submitted to FDA before the date a 505(b)(2) NDA is submitted to the Agency, and typically only a single 30-month stay is available for each 505(b)(2) NDA containing a Paragraph IV certification. Ltr. to Gerald Masoudi, Docket No. FDA-2010-P-0223, at 5 (Oct. 19, 2010).

During the 30-month stay, FDA reviews the follow-on application. While a pending follow-on application may be amended during that review—or supplemented after approval—there are limits to such submissions. Specifically, the FDC Act states that "[a]n applicant may not amend or supplement an application . . . to seek approval of a drug that is a different drug that the drug identified in the application as submitted to the Secretary." 21 U.S.C. § 355(b)(4)(A). FDA has interpreted this provision to prohibit "an applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that has been modified to have a *different active ingredient, different route of administration, different dosage form, or certain differences in excipients* than the drug proposed in the original submission of the 505(b)(2) application," which "conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see guidance for industry on 'Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees' (December 2004) [the '2004 Bundling Rule']." Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69580, 69635 (Oct. 6, 2016) (emphasis added). Conversely, the statute expressly permits the submission of an amendment or supplement to a pending NDA to seek approval for *a different strength*. 21 U.S.C. § 355(b)(4)(B).

No such permission is granted for a change in indication. Absent direction from Congress on the addition of a new indication to a pending 505(b)(2) NDA, FDA has interpreted its regulations such that "[m]ost requests for approval of a different indication or condition of use by a 505(b)(2) applicant should *not* be made as an amendment to the

505(b)(2) application," in accordance with the 2004 Bundling Rule. The 2004 Bundling Rule sets forth FDA's clear requirements for "what will be considered a separate marketing application." 2004 Bundling Rule, at 1. As explained in UTC's December 2023 letter, the Bundling Rule states:

> If submitted simultaneously in one application, requests for approval of different indications and uses for the same dosage form to be administered by the same route of administration . . . can be regarded, for the purposes of assessing user fees, as one application. . . . *After initial submission, a pending original or supplemental application should not be amended to add a new indication or claim*. . . . If the original application is not yet approved, *a request for approval of other new indications or claims should be submitted in a separate, original application*. If the initial application is approved, the application can be subsequently supplemented to add a new indication.

Id. at 4-5 (emphasis added). This Bundling Rule continues to be cited by the Agency in various documents, including, most recently, in a Standard Operating Procedures and Policies ("SOPP") publication dated *January 2024*. SOPP 8401 Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA), at 12 (Jan. 8, 2024) ("In limited circumstances, an applicant may submit two BLAs/NDAs for the same product that are concurrently reviewed as stand-alone applications with separate [Submission Tracking Numbers ('STNs')]. This occurs when an applicant has a pending BLA/NDA and seeks approval for another reason (for example a different indication or dosage) for the same product (refer to the [2004 Bundling Rule]")). Liquidia did not do this in their current application.

B. Factual Background

As UTC's December 2023 letter explained, UTC is the holder of five NDAs for drug products containing treprostinil, including TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/mL, approved under NDA 022387. FDA initially approved TYVASO on July 30, 2009 for the treatment of Pulmonary Arterial Hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance (the "PAH Indication"). On March 31, 2021, FDA approved Supplement S-017 to the TYVASO NDA for a new indication: "for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability" (the "PH-ILD Indication").

In January 2020, Liquidia submitted a 505(b)(2) NDA seeking approval of YUTREPIA (treprostinil) for the PAH Indication relying on UTC's TYVASO as the listed

drug. Liquidia's YUTREPIA 505(b)(2) NDA contained Paragraph IV certifications to some of the then-listed Orange Book patents for TYVASO, including, in particular, U.S. Patent Nos. 9,593,066 ("the '066 patent") and 9,604,901 ("the '901 patent"). UTC timely sued Liquidia for patent infringement, thereby triggering a 30-month stay on the approval of the YUTREPIA 505(b)(2) NDA that expired on or about October 24, 2022. Liquidia later amended its 505(b)(2) NDA and provided a Paragraph IV certification to a later-listed patent, U.S. Patent No. 10,716,793 ("the '793 patent"), but because that patent was later-listed, the Paragraph IV certification did not result in a 30-month stay. In May 2021, Liquidia responded to a Complete Response Letter ("CRL") from FDA resulting in an amendment to the YUTREPIA 505(b)(2) NDA and additional patent certifications. FDA tentatively approved the YUTREPIA 505(b)(2) NDA for the treatment of PAH, but, due to an ongoing 30-month stay, FDA could not grant final approval for the Liquidia 505(b)(2) NDA.

During the pendency of the 30-month stay for the PAH indication, UTC received approval of the new PH-ILD indication. Supplement Approval, NDA 22387/s-017 (Mar. 31, 2021). In July 2023, Liquidia—fully aware of FDA's Bundling Rule—decided to amend the YUTREPIA 505(b)(2) NDA instead of submitting a new 505(b)(2) NDA to add the PH-ILD indication. In that amendment, Liquidia certified to the Orange Book patent information for TYVASO, and UTC timely sued Liquidia for patent infringement, but the subsequent litigation on the patents covering the new indication—the '793 patent, and U.S. Patent No. 11,826,327 ("the '327 patent")—did not trigger a 30-month stay because those patents were added to the Orange Book for TYVASO after the January 20, 2020 submission of the original YUTREPIA 505(b)(2) NDA. According to the Liquidia Letter, the amendment contained no additional data.

FDA assigned the July 2023 amendment a goal date of January 2024—6 months after submission. In January 2024, however, FDA notified Liquidia that it was not going to issue an action letter in time to meet the . . . PDUFA goal date of January 24, 2024." Liquidia Ltr. at 10.

II. LIQUIDIA'S AMENDMENT MUST BE WITHDRAWN

Liquidia misleadingly suggests that UTC is manipulating the regulatory process to thwart competition, but the real issue here is that Liquidia failed to comply with longstanding, repeatedly applied, and recently reaffirmed FDA requirements (and FDA erred in failing to apply them). FDA's Bundling Rule is clear: a new NDA must be submitted to add a new indication to a pending NDA. Liquidia's attempts to circumvent those requirements by framing FDA's longstanding Bundling Rule as a "recommendation"

and outdated "policy" is unpersuasive. FDA cannot condone Liquidia's disregard of FDA's requirements and thereby allow Liquidia to deprive UTC of its statutorily-enabled right to enforce its intellectual property prior to the market entry of a flood of potentially infringing product.

Liquidia takes the position that FDA's 2016 final rule implementing the MMA ("2016 MMA Final Rule") obviates the Bundling Rule, but FDA repeatedly and consistently has emphasized its continued applicability, including when FDA promulgated the very regulations Liquidia claims to have superseded the Bundling Rule. *See, e.g.*, 81 Fed. Reg. at 69616, 69635 ("This final requirement conforms with FDA's current policy regarding the types of proposed changes to a drug product that should be submitted as a separate application (see guidance for industry on [the Bundling Rule] (December 2004). . ."). Contrary to Liquidia's position, nothing in FDA regulations expressly permits the addition of a new indication to a pending 505(b)(2) NDA, and the one regulation which arguably implies such an amendment might be permissible is applicable only in limited circumstances, such as prescription to over-the-counter switches ("RX-to-OTC"). *See* 81 Fed. Reg. at 69616 ("[W]e expect there would be limited circumstances in which [21 C.F.R. § 314.60(f)(1)] would apply to a 505(b)(2) application."). Liquidia fails to address FDA's explicit re-affirmation of the Bundling Rule's ongoing vitality in the very rulemaking proceeding that Liquidia now claims to have overturned decades of uninterrupted and consistently applied Agency rules.

In short, Liquidia—which appears to be represented by experienced FDA counsel in this matter—knew or should have known that a new 505(b)(2) NDA was required to seek approval of a new indication for YUTREPIA; the preamble to the "superseding" rules is clear. But Liquidia chose not to do so. Rather than administrative bifurcation or continuing review of the improperly filed amendment—the implied solutions suggested in the Liquidia Letter—FDA must withdraw the PH-ILD indication supplement and require Liquidia to submit a new NDA so that UTC can do exactly what Congress intended: File suit in order to litigate patents that are specifically related to the new PH-ILD indication before FDA barrels forward with an approval of the pending amendment for that indication. Any other interpretation would be contrary to the text and structure of the Hatch Waxman Act, FDA's longstanding Bundling Rule, and decades of uninterrupted FDA practice in materially indistinguishable cases.

A. UTC's Letter Submission Was Proper

At the outset, UTC disagrees with Liquidia's insistence that UTC's December 2023 letter should have been submitted to FDA as a citizen petition. UTC's December 2023 letter was properly submitted to FDA and shared with Liquidia at FDA's request.

Liquidia begins its assault on UTC's letter submission by noting that it "was submitted as a 'confidential' letter to FDA" rather than as a citizen petition, but in the same breath Liquidia accepts FDA's offer to participate in FDA's letter exchange process and likewise identifies its submission as "confidential." Liquidia Ltr. at 1, n.2. FDA's letter submission and exchange process is well-established in circumstances like those here, where a company wishes to raise with FDA a discrete, application-specific issue that is likely to lead to litigation with the Agency. Indeed, Liquidia's counsel has used the FDA letter submission process to do just that. *E.g.*, Letter from Scott M. Lassman to Grail Sipes dated Dec. 5, 2017, and Letter from Scott M. Lassman to Grail Sipes dated July 23, 2018, *Braeburn Inc. v. FDA*, No. 1:19-cv-00982 (D.D.C.), ECF Nos. 7-5 and 7-6 (Apr. 9, 2019); *see* ECF No. 7-5, at 2 (providing a "detailed legal analysis and position explaining why any exclusivity awarded to SUBLOCADE must be interpreted narrowly and in a manner that does not block approval of CAM2038 or any of its proposed conditions of use.").

In this case, UTC's counsel, in submitting the UTC Letter to FDA on December 29, 2023, requested an urgent call with FDA to discuss the letter submission and a path forward. Email from K. Karst, Counsel to UTC, to Kim Dettelbach, Office of Chief Counsel, FDA (Dec. 29, 2023) ("In an effort to avoid litigation over this matter, UTC requests a meeting with FDA's Office of Chief Counsel and other appropriate FDA representatives to discuss resolution of the matter. To that end, perhaps we can connect early next week after the holiday to schedule a meeting."). FDA responded and offered to speak with UTC's counsel on January 18, 2024. During the scheduled January 18, 2024 teleconference with FDA's Office of Chief Counsel, UTC's counsel asked FDA how it would like to proceed in seeking to resolve the discrete issue raised in the December 29, 2023 letter submission (and for the avoidance of doubt, UTC promptly would have agreed to submit a citizen petition to the Agency if FDA had asked it do so). Yet rather than asking UTC to withdraw its correspondence and re-file it as a citizen petition, FDA instead asked UTC for permission to share a copy of the December 29, 2023 submission with Liquidia. And UTC promptly agreed to participate in the Agency-requested process. In an email sent the same day as the FDA-UTC teleconference, UTC informed the Agency: "As to your question about sharing the December 29, 2023 correspondence, we discussed and would agree to such an arrangement provided Liquidia agrees to share any response with [UTC]. Please let us know if you decide to go down this road, and prior to sharing our

December letter." Email from K. Karst, Counsel to UTC, to Kim Dettelbach, Office of Chief Counsel, FDA (Jan. 18, 2024).

Liquidia itself did not appear to raise any concerns about the process FDA proposed; to the contrary, it appears to have agreed that the process was appropriate. After all, on January 23, 2024, FDA informed UTC counsel not only that the Agency intended to share the December 29, 2023 letter with Liquidia, but also that Liquidia had agreed to share any response with UTC. Email from Kim Dettelbach, Office of Chief Counsel, FDA, to K. Karst, Counsel to UTC (Jan. 23, 2024) ("FDA plans to share your Dec. 29, 2023 correspondence with Liquidia. Liquidia has agreed to share any response with UTC."). Given FDA's choice to proceed with a traditional letter exchange, and Liquidia's own agreement to participate in that process, its contention that UTC somehow engaged in an "unlawful regulatory process" rings hollow. Liquidia Ltr. at 10. In this case, FDA decided that the best path forward to resolve the issue presented was to initiate the well-established letter exchange process; Liquidia agreed to participate in it. That should be the end of this sideshow.

B. FDA Clearly Requires a New NDA for the Addition of a New Indication

On the merits, Liquidia argues that submission of a new NDA should not be required for its attempt to seek approval for a new indication because the Bundling Rule "has been superseded in relevant part by both the [FDC Act] and FDA's regulations." Liquidia Ltr. at 2. But that simply is not true. FDA, as recently as January 2024, made clear that the Bundling Rule remains in full force and effect. *See, e.g.*, SOPP 8401 Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA), at 12 (Jan. 8, 2024) ("In limited circumstances, an applicant may submit two BLAs/NDAs for the same product that are concurrently reviewed as stand-alone applications with separate STNs. This occurs when an applicant has a pending BLA/NDA and seeks approval for another reason (for example a different indication or dosage) for the same product (refer to the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees) [*i.e.*, 2004 Bundling Rule]")). And indeed, the very rulemaking proceedings that allegedly "supersede[d]" the Bundling Rule expressly direct industry to the Bundling Rule to support the premise that "[m]ost requests for approval of a different indication or condition of use by a 505(b)(2) applicant should not be made as an amendment to the 505(b)(2) application." 81 Fed. Reg. at 69616.

Liquidia does not contest the substance of the Bundling Rule; nor could it, as the Bundling Rule unambiguously states that "[i]f the original application is not yet approved,

a request for approval of other new indications or claims should be submitted in a separate, original application." 2004 Bundling Rule, at 4-5. Instead, Liquidia dismisses it as relevant only to user fees. Liquidia Ltr. at 7. While indeed the 2004 Bundling Rule was issued to establish when new applications are required for purposes of user fees, that history is irrelevant. That the Bundling Rule was developed for user-fee purposes does not negate its substantive import: That a new NDA (with a new NDA user fee) is required in order to seek a new indication.[1] 2004 Bundling Rule, at 4-5. Notwithstanding Liquidia's unsupported protests, the Bundling Rule reflects FDA's *current* interpretation of the governing statute and regulations.

Nor does the 2004 Bundling Rule stand alone. The FDC Act itself and the accompanying legislative history support the Bundling Rule. As Liquidia points out, FDC Act § 505(b)(4) precludes a pending 505(b)(2) NDA—which includes a tentatively approved 505(b)(2) NDA—from seeking "approval of a drug that is a different drug than the drug identified in the application as submitted" but "does not define the term 'different drug.'" Liquidia Ltr. at 12. Yet the very next provision of the statute expressly permits the submission of an amendment "to seek approval of a different strength." 21 U.S.C. § 355(b)(4)(b). It contains no comparable authorization for applicants to add new indications, and there is accordingly no reason to read into the statute a requirement that would abrogate the Bundling Rule and compel FDA to accept amendments to pending 505(b)(2) applications adding new indications. As the courts repeatedly have made clear, the inclusion of one specific permission is the exclusion of another. *See, e.g.*, *Jennings v. Rodriguez,* 583 U.S. 281, 300 (2018) ("That express exception to detention implies that there are no *other* circumstances under which aliens detained under §1225(b) may be released" (citing A. Scalia & B. Garner, Reading Law 107 (2012) ("Negative-Implication Canon: The expression of one thing implies the exclusion of others (*expressio unius est exclusio alterius*)")).

In the context of this case, that isn't just a background canon of statutory interpretation; its applicability is sharply underscored by the legislative history accompanying FDC Act § 505(b)(4). Indeed, the legislative history expressly indicates that the "different drug provision" was not intended to upend the Agency's longstanding Bundling Rule:

1 As noted in both the UTC Letter and the Liquidia Letter, the Bundling Rule was first promulgated in 1993 and then revised in 2004 to its current form. UTC Ltr. at 10, n.27; Liquidia Ltr. at 7.

> Congress d[id] not intend this provision to alter current [FDA's] practice regarding acceptance of supplements to approved new drug applications ("NDAs"), or amendments and supplements to pending and approved abbreviated new drug applications ("ANDAs"). Instead, Congress intend[ed] this provision to reflect the FDA's current practice regarding those changes and variations to both innovator and generic drugs that may be approved under amendments . . . ."

H.R. Rep. No. 108-891, at 835 (2003). Thus, that silence was intended to maintain the FDA's 1993 Bundling Rule.

Rather than giving blanket permission to submit an amendment for a new indication to a pending 505(b)(2) NDA, FDA rulemakings implementing the statute prove that the 2004 Bundling Rule remains applicable. Indeed, each of these documents unambiguously directs applicants to the Bundling Rule for questions as to whether a new 505(b)(2) NDA must be submitted. In the 2015 notice of proposed rulemaking for FDA's implementation of the MMA ("2015 NPRM"), FDA makes no fewer than *five* references to the 2004 Bundling Rule, and the 2016 MMA Final Rule preamble references it twice.[2] All of the instances provide direction from the Agency to consult the Bundling Rule precisely because the Agency *expects* industry to consult and rely on the Bundling Rule to determine whether a new NDA is required. The idea that the 2004 Bundling Rule has been superseded by these rulemakings is simply preposterous.

Despite the clear meaning of the statute in light of settled norms of statutory interpretation and the direction from FDA in its rulemakings, Liquidia argues that FDA regulations nonetheless permit the addition of a new indication in an amendment to its 505(b)(2) NDA. Liquidia is wrong.

Pointing to FDA's definition of a "different drug"—which, statutorily, cannot be included in an amendment to a 505(b)(2)—in 21 C.F.R. § 314.60(e), Liquidia argues that FDA did not intend to preclude the filing of an amendment for a new indication. Liquidia Ltr. at 12. This is because, as Liquidia explains, FDA defined "different drug" only as one that "has been modified to have a different active ingredient, different route of administration, different dosage form, or difference in excipients that requires either a separate clinical study to establish safety or effectiveness or, for topical products, that requires a separate in vivo demonstration of bioequivalence." 21 C.F.R. § 314.60(e).

2 *See* 80 Fed. Reg. at 6823, 6849, 6850, 6851, and 6874; *see also* 81 Fed. Reg. at 69616, 69635.

These, according to Liquidia, are the only types of changes to a 505(b)(2) that cannot be submitted in an amendment. Liquidia Ltr. at 12. This argument, however, ignores the final sentence of that provision, which states: "*However, notwithstanding the limitation described in this paragraph (e), an applicant may amend the 505(b)(2) application to seek approval of a different strength.*" 21 C.F.R. § 314.60(e) (emphasis added). That sentence provides an express authorization for a different strength to be submitted in an amendment but says *nothing* about a new indication; if FDA had intended to authorize the addition of new indication through an amendment, it just as easily could have said that. Applying Liquidia's own logic, the absence of a new indication from the second half of the provision supports UTC's position that an amendment *cannot* be submitted for a new indication. Thus, at best, the regulation is a wash, but it assuredly provides no concrete support for Liquidia's claims.

Despite the limitations of the argument, the Liquidia Letter makes much of the omission of a new indication from the definition of a "different drug." It implies that FDA "specifically considered—and rejected—proposals and interpretations" that would have considered a new indication a "different drug." *See* Liquidia Ltr. at 12. But Liquidia chooses its words carefully for a reason: FDA considered and rejected proposals related to *labeling* changes, which could include almost any change to a product, but FDA *never* rejected the addition a new indication to the definition of a "different drug." With no evidence that FDA or Congress considered and rejected a new indication in the definition of a "different drug" and without specific permission for an amendment submission (like for a change in strength), Liquidia's attempt to invoke 21 C.F.R. § 314.60(e) falls well short of the mark.

The same analysis applies to 21 C.F.R. § 314.60(b). These regulations, governing the submission of major amendments, specifically prohibit the submission of a major amendment that includes "data to support an indication or claim that was not included in the original NDA;" it may, however, include data "to support a minor modification of an indication or claim that was included in the original NDA . . . ." 21 C.F.R. § 314.60(b)(6). To the extent that Liquidia's amendment *does* include new data (whether by disclosing Liquidia data or by referencing UTC's TYVASO® NDA to rely on UTC clinical data regarding PH-ILD), 21 C.F.R. § 314.60(b)(6) *compels* the submission of a new NDA, and thus Liquidia's amendment independently violates this regulation. For example, although Liquidia asserts that its amendment did not include any data to support its new request for approval of the PH-ILD indication, Liquidia Ltr. at 9, the amendment seeking approval of such an indication necessarily references and relies upon UTC's INCREASE Phase 3 clinical study, submitted by UTC in support of its own supplemental NDA adding the PH-ILD indication. Information as to that study was not included in Liquidia's original

application. To the extent that Liquidia's application actually contains no clinical data to support the PH-ILD indication, then it is facially deficient under 21 C.F.R. § 314.50(d)(5)(v).

In any event, nothing in these regulations affirmatively *permits* the submission of an amendment for a new indication where data is not required to support it. *Id.* Although 21 C.F.R § 314.60(f)(1) does appear to contemplate that an amendment for a new indication may be submitted in certain circumstances, FDA itself repeatedly emphasized that the scope of this narrow exception is exceptionally "limited." *See* 81 Fed. Reg. at 69616 (discussing the need for additional certifications under 21 C.F.R. § 314.60(f)(1) and stating that "we expect there would be limited circumstances in which this provision would apply to a 505(b)(2) application"). Indeed, both the 2015 NPRM and the preamble to the 2016 MMA Final Rule make very clear that 21 C.F.R. § 314.60(f)(1) applies only in narrow circumstances. The 2015 NPRM states that "most requests for approval of a different indication or condition of use by a 505(b)(2) applicant could not be made as an amendment to the 505(b)(2) application." Proposed Rule, Abbreviated New Drug Applications and 505(b)(2) Applications, 80 Fed. Reg. 6802, 6849 (Feb. 6, 2015). While the 2015 NPRM recognized that "there are certain scenarios in which an applicant may submit an amendment to a 505(b)(2) application (or ANDA) for a new indication or condition of use," FDA noted only a single circumstance in which doing so might be permissible: Where the "indication has changed from prescription status to OTC use." *Id.* The 2016 MMA Final Rule takes the same position, noting that "[m]ost requests for approval of a different indication or condition of use by a 505(b)(2) applicant should not be made as an amendment to the 505(b)(2) application" and that "there would be limited circumstances in which [an amendment to add a new indication] would apply to a 505(b)(2) application (e.g., indication changed from prescription status to OTC use.)" 81 Fed. Reg. at 69616. In other words, it is abundantly clear that this narrow proviso for an amendment to add an indication is a carefully circumscribed exception to the general rule that such amendments are impermissible. Liquidia's reading of the regulations, however, would make this narrow window wide enough to drive a truck through.

To be clear, *nothing* in the 2004 Bundling Rule conflicts with FDA's regulations or the statute; the Bundling Rule merely clarifies. The notion that the Bundling Rule has been "superseded" and "trump[ed]" by these regulations, *see* Liquidia Ltr. at 2, 13, is misleading, unsupported, and nonsensical. And, in fact, FDA's most recent Manual of Policies and Procedures ("MAPP") for NDA Classification Codes, updated in December 2022, has a code specifically for these types of NDAs for new indications, anticipating that they will be filed. FDA, MAPP 5018.2, at 6 (Dec. 8, 2022). That MAPP notes "Generally,

a Type 9 NDA is submitted as a separate NDA so as to be in compliance with the [2004 Bundling Rule]." *Id.*

Liquidia seems to believe that its amendment is somehow special enough not to trigger the 2004 Bundling Rule and is thus exempt from its requirements. But Liquidia has failed to show any reason why its NDA is not subject to the Bundling Rule. Absent an exemption from the Bundling Rule, 21 C.F.R. § 314.60(f)(1) is inapplicable, because, as FDA explained, "most requests for approval of a different indication or condition of use by a 505(b)(2) applicant could not be made as an amendment to the 505(b)(2) application . . . ." 80 Fed. Reg. at 6849. As noted, FDA was clear in its preambles that an amendment to a pending NDA for a new indication is reserved for exceptional circumstances, and Liquidia highlights no reason why its NDA is exceptional.

C. A New 30-Month Stay Logically Follows the Addition of a New Indication

Liquidia positions UTC's request as an anticompetitive attempt to usurp an undeserved additional 30-month stay in "nothing more than an 11th hour attempt to delay the approval" of a competitor, *see* Liquidia Ltr. at 1, but this blatantly mischaracterizes UTC's position. UTC is simply asking that Liquidia (and FDA) follow the law so that UTC can do exactly what Congress wanted: File suit and allow the parties to obtain clarity about their patent dispute prior to a drastic change in the marketplace. That's the tradeoff Liquidia accepted when it shortcut its own approval process by relying on TYVASO data. Liquidia may not like that, but FDA and Congress have repeatedly emphasized that the 30-month stay is a critical element of the Hatch-Waxman Act that was intended to aid *both parties* by providing certainty before any launch. That Liquidia is willing to risk that certainty—and treble damages for willfully infringing UTC's patents—for an earlier launch date is its prerogative, but Liquidia's decision not to follow the law (and FDA's failure to correct that error) is not a legitimate basis for ignoring the delicate balance Congress struck between the interests of generics in launching earlier and the intellectual property rights of brand manufacturers.

The importance of the 30-month stay for the effective application of the Hatch-Waxman Act cannot be overstated. Congress created the 30-month stay "not necessarily to extend the patent holder's monopoly, but to create an adequate window of time during which to litigate the question of whether a generic will infringe the patented product, without actually having to introduce the generic product to the market." *Ben Venue Labs. Inc. v. Novartis Pharm. Corp.*, 146 F. Supp. 2d 572, 579 (D. N.J. 2001). That 30-month period, intended both to give assurance to the innovator that a follow-on drug manufacturer

would not obtain approval and market its product until the patent is litigated and to remove the risk that brands would hold patents in reserve and thereby lead generics to delay the launch of approved drugs because of patent uncertainty, was critical to the "compromise" that allowed the Hatch-Waxman Act to be enacted. 130 Cong. Rec. H9118 (daily ed. Sept. 6, 1984) (statement of Rep. Waxman) (explaining the support for a 30-month stay rather than an 18-month stay).

As FDA explained in adopting its 2016 MMA Final Rule regulations, "[o]ur interpretation of section [FDC Act § 505(b)(4)] seeks to preserve the legislative balance of the Hatch-Waxman Amendments with respect to facilitating the availability of drug products that meet the statutory requirements for approval while protecting innovator intellectual property rights (and allowing for an early resolution of any patent infringement litigation)." 80 Fed. Reg. at 6851. While this discussion was in the context of FDA's interpretation of "different drug," FDA's logic is equally applicable to a new indication: "Consistent with FDA's 'bundling' policy in effect at the time of enactment of the MMA," changes listed in the 2004 Bundling Rule "are significant enough that it is reasonable to assume that one or more patents for the listed drug might be implicated by the change and, if an action for patent infringement is brought in response to a paragraph IV certification to a listed patent, an opportunity for 30-month stay would be appropriate." 80 Fed. Reg. at 6851. The situation here clearly was not anticipated by the statute, but it was anticipated by FDA, which is exactly why FDA has been clear that most changes to indications will require a new NDA.

And an additional 30-month stay here simply makes sense. The intent of the bar on 30-month stays for later-listed patents assumes that the later-listed patents could have covered the product at approval. Where a new indication is developed and approved, the relevant patents can be listed only after approval of the new indication. These patents, even though they are "later-listed," cover the new aspects of the product that only became relevant because of an additional approval; such patents are not the same as, and cannot be treated the same as, later-listed patents that could have been listed at approval, had they been issued. This, again, is precisely why FDA requires new NDAs where a change to the product might implicate other patent rights. The absence of a 30-month stay for a patent covering a newly-approved condition of use provides no opportunity for the innovator to protect its intellectual property on that indication without immediate competition. This not only disrupts the balance intended by the Hatch-Waxman Act, but it also undermines patent protections covering the further development of existing drugs, diluting incentives to repurpose older drugs.

In this case, the absence of a 30-month stay would allow Liquidia to flood the market with an infringing product—a bell that cannot be unrung even in the face of treble damages.

D. FDA Must Withdraw the Liquidia PH-ILD Amendment

Liquidia argues that the 2004 Bundling Rule does not require FDA to refuse to file or review the pending NDA. But even if FDA may sometimes excuse minor, inadvertent errors under the Bundling Rule, Liquidia's clear disregard of unambiguous FDA policy to avoid the requirements of the Hatch-Waxman Act cannot be countenanced. Nor can the FDA disregard Liquidia's violation of binding regulations. *See* 21 C.F.R. §§ 314.50(d)(5), 314.60(b)(6). At a minimum, nothing in the Bundling Rule precludes FDA from requiring Liquidia to file an NDA rather than an amendment—and nothing in the rule permits FDA to approve the amendment in its improper form. That FDA erred in accepting an amendment unlawfully submitted by Liquidia in the first instance provides no justification for the agency to compound that error by continuing review of or approving the unlawful submission, particularly in a situation that would undermine the essential bargain at the heart of Hatch-Waxman. And FDA clearly has the authority to mandate withdrawal of the amendment that it never should have accepted in the first place. *See Ranbaxy Labs., LTD v. Burwell*, 82 F. Supp. 3d 159, 193 (D.D.C. 2015) (holding that the Agency has the ability to correct its administrative errors to ensure that the FDC Act's "statutory purpose is followed"); *Ivy Sports Medicine, LLC v. Burwell* (*Ivy Sports*), 767 F.3d 81, 86, 412 U.S. App. D.C. 452 (D.C. Cir. 2014) ("[A]dministrative agencies are assumed to possess at least some inherent authority to revisit their prior decisions . . . .").

The Liquidia Letter urges FDA not to withdraw the amendment on the theory that, essentially, this is a harmless error; but this is neither harmless nor, on Liquidia's part, an error. First, Liquidia, advised by counsel and led by experienced pharmaceutical executives, knew or should have known that a separate NDA submission was required by FDA. Even a cursory reading of the Bundling Rule and the 2015 NPRM and 2016 MMA Final Rule preambles makes that clear. Second, even if it were simply an error, it is far from harmless: UTC is being deprived of the opportunity to take advantage of an important statutory protection, which includes the opportunity to enforce its patents before the market is overrun with infringing product.

Rather than withdrawal and submission of a new 505(b)(2) NDA, Liquidia also suggests administrative bifurcation of the NDA, assigning the new indication a submission date of July 2023. But this would reward Liquidia for its nonconformance to plain FDA requirements. Indeed, Liquidia's proposed solution results in the avoidance of the timely-submitted patents, which, other than ignorance of controlling law, is the only plausible

reason that Liquidia submitted an amendment to add the PH-ILD indication rather than submitting a new NDA to begin with. Liquidia should not be rewarded for its avoidance of well-known FDA requirements.

That Liquidia claims it will refuse to submit a new NDA is immaterial to the discussion at hand. This is not about what Liquidia is willing to do but what the law requires FDA to do. Here, the law requires FDA to rectify this situation and restore UTC's Hatch-Waxman rights. In this case that means FDA must consider Liquidia's July 24, 2023 PH-ILD Indication amendment null and void and require Liquidia to submit a new original 505(b)(2) NDA with certifications to patent information currently listed in the Orange Book for the TYVASO Listed Drug (*i.e.*, as of the date Liquidia submits a new original 505(b)(2) NDA for the PH-ILD Indication).

E. FDA Must Treat Similar Applicants Similarly

Liquidia dismisses the multitude of examples cited in UTC's previous letter as inapt, as more recent examples involve amendments to applications for reasons other than changes in indication. But Liquidia misses the point: Liquidia insists that the 2004 Bundling Rule is just a recommendation, non-binding on the Agency, and cannot be the source of an Administrative Procedure Act argument that FDA is treating similarly-situated applications dissimilarly. *See* Liquidia Ltr. at 14 ("[T]he 'litany' of examples provided in the UTC Letter are . . . inapplicable to the July Amendment."). The point is that FDA has consistently applied the Bundling Rule for more than 30 years. Liquidia's argument that the Bundling Rule is inapplicable because it is superseded by regulation is proved incorrect by the continued application of that rule. *See* UTC Ltr. at 11. In other words, it is not the treatment of the specific applications referenced that render the applicants similar—it is the fact that the 2004 Bundling Rule was equally applied in all situations covered by that rule that makes the situations comparable. Timing, type of application, and type of change are all irrelevant; what is relevant is that FDA applied the 2004 Bundling Rule as written to all of those applications. There is no reason that Liquidia should not also have followed the Bundling Rule, or that FDA should not apply the rule to Liquidia.

III. CONCLUSION

As explained in our December 29, 2023 letter, FDA has, for decades, applied the Bundling Rule to require the submission of a new NDA to add a new indication. Liquidia depicts the Bundling Rule as an outdated, superseded recommendation, but this obfuscates FDA's continued reliance and reference to the Bundling Rule. There is no reason that Liquidia would not have known that a separate NDA is required for such a change, and

Liquidia cannot be rewarded for its duplicity with acceptance of that amendment as of July 2023. To be consistent with its rulemakings, its policies, congressional intent, and its history of enforcement as described in our earlier letter, FDA must consider Liquidia's July 2023 amendment null and void and require the company to submit a new 505(b)(2) NDA for the PH-ILD indication.

###

We look forward to hearing from FDA on this matter. To that end, FDA's failure to take prompt action consistent with the Bundling Rule, and to UTC's satisfaction, will leave UTC with no other option than to initiate litigation against FDA.

Respectfully submitted,

Kurt R. Karst
Michael D. Shumsky
Sara W. Koblitz
Counsel for United Therapeutics Corporation

EXHIBIT 14

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, Inc.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
U.S. Patent No. 10,716,793

PATENT OWNER RESPONSE

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I. INTRODUCTION

Liquidia Technologies, Inc. ("Petitioner") has failed to meet its burden of proving claims 1-8 of U.S. Patent No. 10,716,793 ("the '793 patent") are unpatentable because it relies on references that are not, in fact, prior art and bases its arguments on impermissible hindsight rather than teachings in the prior art.

First, each of Petitioner's six unpatentabily grounds rely upon references that Petitioner has failed to establish constitute prior art. Grounds 1, 2, and 4 expressly rely on Voswinckel JESC and/or Voswinckel JAHA, but Petitioner has not set forth sufficient evidence to show that either abstract was publicly accessible as of the priority date of the claimed inventions. Grounds 3-6 expressly rely on Ghofrani and/or Voswinckel 2006, but Petitioner has not set forth sufficient evidence to show that either of these references are antedating or "by others." This fundamental failure of proof is fatal to Petitioner's case-in-chief.

Second, Petitioner's unpatentability grounds based on the combination of the '212 patent, Voswinckel JESC, and/or Voswinckel JAHA cobble together bits of disclosure guided by impermissible hindsight and expert declarations that rely on unsupported assumptions and unreliable calculations. None of these references disclose administration of a single event dose from 15-90 μg to a human, let alone delivery of that dose in 1-3 breaths. The '212 patent discloses sheep data delivered over 30 or more minutes. Voswinckel JESC and JAHA disclose concentrations, but

not single event doses. Petitioner therefore cites an undated device manual that Petitioner has not proven was publicly available and relies on assumptions of its experts in an attempt to calculate a single event dose. The POSA, however, would not perform these calculations and the calculations are flawed. Without disclosure of the claimed single event dose, Petitioner's grounds fail.

Accordingly, Petitioner has not carried its burden to prove unpatentability and the claims are patentable over all of the cited grounds.

II. BACKGROUND

The '793 patent relates to the treatment of pulmonary hypertension and is listed in the Orange Book for Tyvaso® (treprostinil) Inhalation Solution, a drug-device combination for delivery of treprostinil by inhalation marketed by Patent Owner, United Therapeutics Corporation ("UTC"). EX1001, 18:22-23; EX2007.

A. Pulmonary Hypertension

Pulmonary hypertension is a disease associated with high blood pressure in the pulmonary vasculature. *See generally* EX2050. At the time of the invention, as is the case even today, pulmonary hypertension is a poorly understood, often fatal, disease with limited treatment options.

Epoprostenol is a prostacyclin and was the first and only FDA-approved drug for the treatment of pulmonary arterial hypertension ("PAH") from 1995 to 2001. EX2051. The use of epoprostenol had substantial shortcomings. The half-life of

epoprostenol is only a few minutes, meaning that it is cleared from the body very quickly has a short duration of action. EX2008, 7-10. Thus, epoprostenol required administration by continuous intravenous infusion to maintain adequate levels in the body. Unfortunately, the need for a permanent transcutaneous intravenous catheter posed risks of infection, occlusion, and sepsis. Moreover, even a short interruption in infusion could increase the risk of hemodynamic collapse and even death because the half-life of epoprostenol is so short. Epoprostenol also requires daily mixing and refrigeration, which meant the patient must carry a cold pack to avoid degradation at room temperature and an infusion pump to administer the drug, which adversely affect patient compliance.

In 2004, a synthetic prostacyclin analog, iloprost (Ventavis®), was approved as an inhaled treatment for PAH. *Id.* at 10. Although inhaled iloprost had a slightly longer duration of action than epoprostenol, doctors still preferred intravenous administration of a prostacyclin analog over inhaled delivery of iloprost for a number of reasons. *Id.* For instance, iloprost has a half-life between 20-25 minutes and needs to be used 6-9 times a day, as frequently as every 2 hours, which is considered challenging for patients. *Id.* at 21, 23-24. Moreover, the fact that iloprost has a short half-life results in periods of patients being under-medicated while asleep unless they wake at regular intervals to take another dose. *Id.*

Treprostinil, the compound described in the '793 patent, was approved to treat PAH as a subcutaneous formulation (Remodulin®) by 2002 and for intravenous use in 2004. *Id.* Treprostinil offered benefits over both epoprostenol and iloprost such as room temperature stability and a half-life of several hours versus several minutes. Patients no longer needed to carry ice packs to ensure the stability, safety, and efficacy of the drug. *Id.* However, there were still significant limitations to subcutaneous and intravenous delivery of treprostinil, such as severe site pain for some patients, and systemic side effects. EX1018, 1.

B. The Inventors Developed a Novel Method of Treating PAH That Overcame Limitations of Existing Treatments

At the time of the invention, the inventors recognized a need for improving existing pulmonary hypertension treatments. The '793 patent relates to a breakthrough method of treating pulmonary hypertension using high dose administration of inhaled treprostinil that addressed many of the substantial shortcomings of other existing treatments. The '793 patent claims methods of treating pulmonary hypertension using a single event dose of 15-90 micrograms of treprostinil, or a salt thereof, delivered by inhalation in only 1 to 3 breaths. By using the inhalation route of administration, the claimed methods overcame limitations to subcutaneous and intravenous administration, such as site pain injection, systemic side effects, and the need for patients to lug around bulky pumps. The inventors also improved the safety and efficacy of treatment with the surprising discovery that

treprostinil could be delivered at higher drug concentrations and shorter inhalation times (3 breaths) with fewer side effects.

The ’793 patent issued from an application filed on January 31, 2020 and claims priority to a provisional application, 60/800,016, filed on May 15, 2006. Petitioner does not contest this priority date.

The ’793 patent has 1 independent claim and 7 dependent claims. Independent claim 1 recites:

> A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

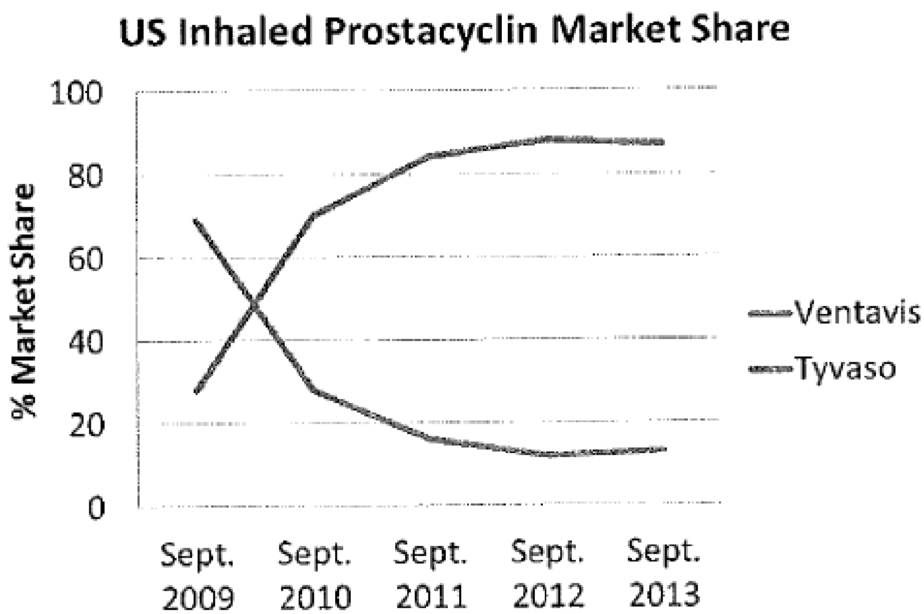
EX. 1001, claim 1. Dependent claims 2 through 5 require specific types of inhalation devices, namely a soft mist inhaler (claim 2), a pulsed ultrasonic nebulizer (claim 3), a dry powder inhaler (claim 4) or a pressurized metered dose inhaler (claim 5). Dependent claim 6 requires the formulation to be a dry powder, and dependent claim 7 requires the powder to comprise particles less than 5 micrometers in diameter. Dependent claim 8 requires the formulation to contain no metacresol.

The ’793 patent teaches that administration of treprostinil using the claimed methods resulted in a significant reduction in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) and an increase in cardiac output. EX1001,

FIG. 10; 16:32-42. The specification describes the surprising result of clinical studies showing that the time of inhalation could be reduced by increasing the concentration of treprostinil aerosol. *Id.* at 16:61-63, 17:44-46. This single-breath drug administration induced pulmonary vasodilation for longer than 3 hours with minimal side effects. *Id.* at 18:1-6. Surprisingly, very high concentrations of treprostinil were well tolerated (*id.*), even though initial clinical trials showed that increasing concentration from 16 mcg/ml to 64 mcg/ml led to significant side effects without increasing pulmonary vasodilation. EX1007 (at 16 mcg/ml, "near maximal pulmonary vasodilation is achieved without adverse effects").

The commercial embodiment of the '793 patent, Tyvaso® (treprostinil) Inhalation Solution, has shown distinct advantages over the other available treatments for pulmonary hypertension. Tyvaso® has a much longer half-life than Ventavis®. Thus, there is less risk of undermedication when the patient is asleep or otherwise unable to take the medication. Additionally, Tyvaso® does not need to be administered as frequently as Ventavis® (only 4 times a day, down from 6-9 times/day). Less frequent dosing leads to higher patient compliance, time savings of 1.4 hours per day (EX2052, ¶43) and lower risk of rebound hypertension. Patients transferring from inhaled iloprost to inhaled treprostinil also had improved six-minute walk distances (a common metric to assess pulmonary hypertension), improved patient satisfaction, and improved quality of life. *Id.* at 8-9. Notably, once

Tyvaso® entered the market, it was clinically preferred to Ventavis®. As illustrated below, Tyvaso® rapidly increased its market share after launch at Ventavis®'s expense, indicating the clinical advantages that Tyvaso® has over Ventavis®:



EX2086, ¶18.

III. CLAIM CONSTRUCTION AND PERSON OF ORDINARY SKILL

The parties agree that all claim limitations of the '793 patent should be given their plain and ordinary meaning in the art by a person of ordinary skill in the art (POSA) as of May 15, 2006.

A POSA, with respect to the '793 patent, would have an M.D. or a graduate degree (Masters or Ph.D.) in a field relating to drug development and at least two years practical experience in either (i) the investigation or treatment of pulmonary

hypertension; or (ii) in the development of potential drug candidates, specifically in the delivery of drugs by inhalation. EX2052, ¶¶13-16; EX2053, ¶¶28-31.

IV. PETITIONER HAS NOT MET ITS BURDEN TO ESTABLISH THAT CLAIMS 1-8 OF THE ’793 PATENT ARE ANTICIPATED OR OBVIOUS

Petitioner has “the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316I; *see also* 37 C.F.R. § 42.108. Petitioner has failed to carry that burden for any of its six Grounds:

Ground 1 (Claims 1-8): Obvious over ’212 Patent, Voswinckel JESC, and Voswinckel JAHA
Ground 2 (Claims 1-8): Obvious over ’212 Patent and Voswinckel JESC
Ground 3 (Claim 1): Anticipated by Ghofrani
Ground 4 (Claims 1, 3, and 8): Obvious over Voswinckel JAHA and Ghofrani
Ground 5 (Claims 1 and 3): Anticipated by Voswinckel 2006
Ground 6 (Claims 2 and 4-8): Obvious over Voswinckel 2006 and the ’212 Patent

Grounds 1 and 2 rely upon a combination of the ’212 patent and Voswinckel JESC (Ground 2) and in further view of Voswinckel JAHA (Ground 1). Petitioner has failed to show that Voswinckel JAHA and Voswinckel JESC were publicly accessible prior art. Even setting aside this fatal flaw, none of the references

expressly teach a "single event dose"[1] of "15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths." In an effort to fill this gap, Petitioner relies on flawed calculations and assumptions and an undated Operating Instruction Manual (EX1037) for a device referred to by Petitioner as "Optineb 2005." Pet., 23; *see also, e.g.*, EX1004, ¶¶74, 108; EX1002, ¶47.[2] In addition to improperly relying on the undated OptiNeb Manual, the POSA would not be able to calculate a delivered dose based on the scant information in Voswinckel JAHA or JESC, let alone with any reasonable accuracy. Accordingly, Petitioner cannot meet its burden of establishing that the '212 patent, Voswinckel JESC and/or Voswinckel JAHA teaches or suggests the claimed dose or that a POSA would have been motivated to combine the teachings of these prior art references to achieve the claimed invention with a reasonable expectation of success.

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[1] A POSA would understand "single event dose" to mean the dose administered in one sitting, which could be one or multiple breaths. EX2053, ¶50 n.5; EX2052, ¶48 n.4.

[2] Both Drs. Gonda (EX1004, ¶108) and Hill (EX1002, ¶47) rely on the specification of the '793 patent as disclosing that a "pulsed" feature of the Optineb device was known, but the modifications that gave rise to this "pulsed" feature in the Optineb device are not prior art. EX2003, ¶26.

Further, Grounds 3 through 6 explicitly rely on Ghofrani and/or Voswinckel 2006. Ghofrani and Voswinckel 2006 do not qualify as prior art under § 102(a) because they are not "by another" as Drs. Seeger, Ghofrani, Reichenberger, and Grimminger explain, the information relied upon by Petitioner for these two references was solely the work of the inventors of the '793 patent. As discussed below, these references are also antedated because the claimed invention was invented prior to the publication date of Ghofrani and Voswinckel 2006 and are thus, not qualifying prior art.

A. Ground 1: the '212 Patent, Voswinckel JESC, and Voswinckel JAHA Fail to Render Claims 1-8 Obvious

The Petition fails to establish by a preponderance of the evidence that any of the challenged claims are invalid as obvious over the combination in Ground 1 for several reasons. First, Petitioner has not set forth sufficient evidence to show that Voswinckel JAHA and Voswinckel JESC were publicly accessible prior art. Specifically, Petitioner failed to establish that either of these abstracts were received by a library before the priority date. Furthermore, Petitioner failed to identify how a POSA could allegedly locate these abstracts through the exercise of reasonable diligence before the priority date. To the contrary, the evidence shows that the Voswinckel JAHA and Voswinckel JESC abstracts are not indexed and difficult to find even today.

Second, none of the cited prior art references teaches or suggests a "single event dose" of "15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths." The '212 patent specified a broad range of delivered doses, but on a per kilogram and a per minute basis – not a total dose delivered. Voswinckel JESC and Voswinckel JAHA only provide the initial concentration of a pre-aerosolized drug solution and the length of time that the drug is inhaled. As explained in more detail below, the single event dose delivered for any given patient using an inhalation device depends upon numerous factors relating to the type of inhalation device used and use by the patient. The information provided by Voswinckel JESC and Voswinckel JAHA is insufficient for a POSA to determine what single event dosage was administered. Only impermissible hindsight fills this hole in the references.

Third, Petitioner has failed to show that a POSA would have had a reasonable expectation of success for treatment of a patient with pulmonary hypertension by modifying the dosage ranges of the '212 patent to achieve a single event dose of 15 micrograms to 90 micrograms in 1 to 3 breaths.

1. Petitioner Has Not Established That Voswinckel JAHA And Voswinckel JESC Were Publicly Accessible Prior Art Before The Priority Date

The determination of whether a document is a "printed publication" that qualifies as prior art hinges on "public accessibility." *Blue Calypso, LLC v.*

Groupon, Inc., 815 F.3d 1331, 1348 (Fed. Cir. 2016) (quoting *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986)). Public accessibility is the "touchstone in determining whether a reference constitutes a printed publication," and a reference is considered publicly accessible only if it was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (internal citations omitted).

For references stored in libraries, public accessibility requires that the reference be both available at the library and sufficiently indexed or catalogued by the priority date. *Blue Calypso, LLC v. Groupon, Inc.,* 815 F.3d 1331, 1348 (Fed. Cir. 2016); *In re Klopfenstein,* 380 F.3d 1345, 1349 (Fed. Cir. 2004). In many circumstances, whether a reference is publicly accessible will turn on whether it was "meaningfully indexed such that an interested artisan exercising reasonable diligence would have found it." *Acceleration Bay, LLC v. Activision Blizzard Inc.,* 908 F.3d 765, 774 (Fed. Cir. 2018).

a) No Evidence That A Library Received Voswinckel JAHA Or Voswinckel JESC Before The Priority Date

Petitioner has failed to show that either Voswinckel JAHA (EX1008) or Voswinckel JESC (EX1007) were received by a library before the priority date. Neither reference contains a "received by" or "accepted" stamp or notation and

Petitioner's expert, Dr. Hall-Ellis, admitted the same. *See generally* EX1007; EX1008; EX2043, 150:16-23; EX2041, ¶¶13, 18-19, 33.

Dr. Hall-Ellis' reliance on the publication frequency for the journal *Circulation* and the *European Heart Journal* does not establish the public availability of the relevant abstracts appearing in the *supplements* of those journals. *See* EX2041, ¶¶10-14, 30-33. Voswinckel JAHA and Voswinckel JESC are abstracts appearing in special supplements of the journal *Circulation*, published by the American Heart Association (the "Circulation Supplement"), and the *European Heart Journal*, published by the European Society of Cardiology ("EHJ Supplement"), respectively. *Id.*, ¶¶6, 10, 28, 30; *see also* EX2043, 108:15-25, 219:1-23. The *Circulation* and *EHJ* Supplements are not normal issues, and instead constitute irregularly published supplements, each containing thousands of disjointed abstracts. *Id.*

Importantly, supplements compiling conference abstracts can sometimes publish years after the conference in question, putting the *Circulation* and *EHJ* Supplements' availability (if any) past the priority date. EX2041, ¶¶10-11, 30-31. Thus, the publication frequencies for normal issues of *Circulation* and *EHJ* do not establish when a library might have received a print copy of the irregularly published supplements. *Id.* at ¶¶9-14, 29-33. Accordingly, Petitioner has not provided any evidence showing if or when *Circulation* and *EHJ* Supplements were actually

received by a library. *Id*. at ¶¶14, 27, 33; *see also* EX2043, 150:16-151:7, 157:6-11, 217:11-13, 222:1-10.

Library Machine-Readable Cataloging ("MARC") and Library of Congress ("LOC") records containing metadata fields cited by Dr. Hall-Ellis likewise fail to establish when the *Circulation* or *EHJ* Supplements were publicly accessible. All of the records provided by Dr. Hall-Ellis relate only to the journal *Circulation* and the *EHJ* – *i.e.*, the publications at large, comprising all published issues spanning decades – not the *Circulation* and *EHJ* Supplements that actually contain the Voswinckel JAHA and JESC abstracts. *See* EX1036, ¶¶63, 69; *see also* EX2043, 157:1-5, 222:12–224:2; EX2041, ¶¶20-22, 34-35. Because the metadata fields in MARC and LOC records cited by Dr. Hall-Ellis also relate to the entire journals Circulation and the EHJ, the records do not establish receipt of the *Circulation* or *EHJ* Supplements before the priority date. *Id.*

b) Insufficient Evidence that Voswinckel JAHA and JESC Could Have Been Located with Reasonable Diligence

Even assuming Voswinckel JAHA and JESC were received by the University of Wisconsin-Madison and University of Iowa libraries, respectively, before the priority date, Petitioner has still failed to show that the abstracts were meaningfully catalogued and indexed before the priority date such that a POSA could have located

them through reasonable diligence.[3] *Acceleration Bay*, 908 F.3d at 774. There are two major shortcomings with Petitioner's alleged evidence.

First, Petitioner has not offered any evidence that Voswinckel JAHA and Voswinckel JESC were meaningfully catalogued or indexed at a library or in a database before the priority date, or why and how a POSA would search for or find the *Circulation* and *EHJ* Supplements. *See* EX2041, ¶¶16-17, 34-37. Even if a POSA found the Supplements, Voswinckel JAHA shares the page with three-and-a-half other abstracts and is just one of many thousands of abstracts spanning 1,102 pages in the full version of the *Circulation* Supplement. *Id.* at ¶10. Petitioner has not submitted any evidence that the *Circulation* Supplement contained a table of contents or subject matter index through which the cited abstract (number 1,414) could be located. *Id.* at ¶¶7-8, 25-26. Similarly, Voswinckel JESC cited by Petitioner shares the page with three other abstracts and is just one of 3,850 abstracts spanning over 700 pages in the full version of the *EHJ* Supplement. *Id.* at ¶28. Although there is a list of "Contents" included within Voswinckel JESC, it is not

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[3] The Federal Circuit has held that proof of indexing in a "meaningful way," together with evidence that the indexing occurred by the critical date, may be necessary before the burden shifts to Patent Owner to prove otherwise. *In re Lister*, 583 F.3d 1307, 1312 (Fed. Cir. 2009).

organized alphabetically or otherwise ordered by subject. *Id.* at ¶35. As a result, Petitioner has not shown that the POSA could locate either Voswinckel JAHA or JESC using reasonable diligence.

To the contrary, it is undisputed that Voswinckel JAHA and Voswinckel JESC remain difficult to find even today. For example, Dr. Hall-Ellis admitted she either did not search for Voswinckel JESC using typical searches, such as through a common database like PubMed,[4] or was unable to locate Voswinckel JESC. *See* EX2043, 242:11–245:22. Ms. Wyman searched all of the databases cited by Dr. Hall-Ellis (*see id.* at 41:1-42:4; 242:11-243:18 (listing Ovid, PubMed, MEDLINE, Index Medicus, and Chemical Abstracts)), but neither abstract is listed in any of these databases today, and Petitioner has failed to show they were listed in 2006. EX2041, ¶¶5, 16-17, 37. Moreover, the *Circulation* Supplement cannot be found on the *Circulation* Journal's website, AHA online archives, or even in a list of supplements to the journal. *Id.* at ¶¶12, 15. Similarly, the *EHJ* Supplement cannot be found on *European Heart Journal's* website or online archives. *Id.* at ¶32.

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[4] PubMed.gov searches "more than 33 million citations for biomedical literature from MEDLINE, life science journals, and online books." *See* PubMed, *available at* https://pubmed.ncbi.nlm.nih.gov/ (last visited Nov. 1, 2021).

Second, the MARC and LOC records cited by Dr. Hall-Ellis do not establish meaningful indexing either. Dr. Hall-Ellis cites two subject headings or descriptor terms, "Cardiology $x Societies" and "Heart $x Diseases $v Periodicals," as alleged evidence of meaningful indexing. EX1036, ¶64. However, these terms only indicate the entire journals themselves were allegedly indexed with these terms and are not unique to the cited abstracts. EX2041, ¶¶20-23, 34-35. *Circulation* has been published for more than 50 years (*id*. at ¶24), and the *EHJ* has been published for about 40 years (*id*. at ¶35), so merely locating the journals would not help a POSA find the Supplements, let alone the specific Voswinckel abstracts buried among many thousands of other disparate abstracts. *Id.* at ¶¶4, 20-24, 34-35. Any searches using Dr. Hall-Ellis' descriptor search terms would be futile as they would return hundreds of thousands of hits, including hundreds of journals having decades of issues.[5] *Id.* at ¶¶4, 23-25, 34-35; *see also* EX2043, 158:5-160:2.

[5] Dr. Hall-Ellis admitted that researchers typically only look at the first three pages of search results, (EX2043, 88:7-9), which confirms the difficulty the POSA would have in locating the Voswinckel abstracts when faced with so many journals, issues, and articles hitting on Dr. Hall-Ellis's search terms.

The law requires Petitioner to provide evidence establishing that Voswinckel JAHA and Voswinckel JESC were received at a library and meaningfully indexed before the priority date.[6] Petitioner's evidence falls far short of that standard (EX2041, ¶¶3-4, 27, 38), and the Board should find that Petitioner has failed to prove that the Voswinckel JAHA and JESC abstracts were publicly accessible prior art.

2. None of the identified references teaches a single event dose of 15 micrograms to 90 micrograms in 1 to 3 breaths

None of the '212 patent, Voswinckel JAHA, or Voswinckel JESC references teach a single event dose of treprostinil of 15 micrograms to 90 micrograms, delivered in 1 to 3 breaths. Petitioner concedes that the '212 patent and Voswinckel JESC do not explicitly disclose these limitations. Pet., 37-39.

a) The '212 patent

U.S. Patent No. 6,521,212 ("the '212 patent") issued February 8, 2003 and is titled "Method for Treating Peripheral Vascular Disease by Administering Benzindene Prostaglandins by Inhalation." The '212 patent teaches methods of delivering benzindene prostaglandins by inhalation generally. EX1006, Abstract. The '212 patent states, "aerosolized treprostinil] has a greater potency as compared to intravascularly administered [treprostinil]." *Id.* at 8:9-10. The '212 patent

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[6] *Blue Calypso,* 815 F.3d at 1348; *Acceleration Bay,* 908 F.3d at 774.

provides examples, wherein intravenous or aerosolized treprostinil is administered to sheep at 30, 60 or 90 minutes at a concentration of 250, 500, or 1000 ng/kg/min. *See, e.g., Id.* at FIGS 3-18, Examples I-V.

The ’212 patent does not teach a single event dose of 15 micrograms to 90 micrograms in 1 to 3 breaths. Instead, the ’212 patent describes a very broad range of dosages delivered over a period of minutes. The disclosed dosages either specify a “daily infusion dose” or “per kilogram bodyweight per minute” dose, which are not inhaled single event doses as claimed by the ’793 patent but *rates* (*e.g.*, µg per unit of body mass per day) or *daily* doses:

> In the case of treating ***peripheral vascular disease*** by inhalation of a benzindene prostaglandin of the present invention, the dosage for inhalation, taking into account that some of the active ingredient is breathed out and not taken into the bloodstream, should be sufficient to deliver an amount that is equivalent to **a daily infusion dose** in the range of 25 µg to 250 mg; typically from 0.5 tg[sic] to 2.5 mg, preferably from 7 µg to 285 µg, **per day per kilogram bodyweight**. For example, an intravenous dose in the range 0.5 µg to 1.5 mg **per kilogram bodyweight per day** may conveniently be administered as an infusion of from 0.5 [µg] to 1.0 µg **per kilogram bodyweight per minute**. A preferred dosage is 10 **ng/kg/min**.

EX1006, 5:56-67 (emphasis added).

Further, the dosages described in the ’212 patent are contemplated for use in a continuous nebulization device. For example, the ’212 patent describes an “AM-601 MEDICATOR AEROSOL DELIVERY SYSTEM” as the preferred device, and it is the only specific device mentioned anywhere in the patent. EX1006, 5:34-36;

EX2052, ¶53. This device is a *continuous* nebulizer designed to deliver small amounts of medication in a dosing event *spread over several minutes using dozens or hundreds of breaths*. EX2087, 2364; EX2052, ¶50. This type of device lacks the precision to deliver a measured amount of drug in the range of 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in only 1 to 3 breaths. EX2052. ¶55.

Similarly, the working examples of the '212 patent use continuous delivery of a treprostinil solution over 30, 60, or 90-minute intervals. EX1006, 10:44, 11:11-13. Treprostinil is delivered at a concentration of 250, 500 or 1000 ng/kg/min. None of these modes of administration disclose or teach a single event dose of 15 micrograms to 90 micrograms. EX2041, ¶52. Nor could a POSA determine the amount delivered in 1 to 3 breaths from the experimental descriptions of Examples I-V. EX2053, ¶¶49-50.

b) Voswinckel JESC

Voswinckel JESC is a quarter-page abstract dated August/September 2004 and titled "Inhaled treprostinil is a potent vasodilator in severe pulmonary hypertension." EX1007. Voswinckel JESC generally describes the delivery of treprostinil over a six-minute interval using an OptiNeb ultrasound nebulizer with a pre-aerosolized starting solution of 16, 32, 48 and 64 μg/mL. EX1007. The abstract observed that "[a]t higher doses, local and systemic side effects may occur." *Id.*

Indeed, all patients who received the 64 µg/mL complained of headache, cough or bronchoconstriction, including one patient who complained of a major headache. *Id.* The reference concludes that, at 16 mcg/ml, "near maximal pulmonary vasodilation is achieved without adverse effects." *Id.* Thus, Voswinckel JESC teaches away from titrating up to higher drug concentrations over an even shorter time interval.

Petitioner admits that Voswinckel JESC does not teach a single event dose of 15 micrograms to 90 micrograms, but instead describe solution concentrations and a nebulization time of 6 minutes[7] that their experts admit lack many details that bear on the actual delivered dose. Pet., 38. As explained in more detail below, the actual dose delivered for any given patient using an inhalation device depends upon a number of factors including the type of inhalation device used, pre-aerosolized drug concentration, gas flow and pressure, fill and dead volumes, gas density, and humidity and temperature conditions. Without accounting for any of these factors, Petitioner relies on unsupported calculations (discussed in section IV.A.3 below), that Petitioner alleges would lead a POSA to the claimed dosage range.

[7] A POSA would understand that the plain and ordinary meaning of the claimed dose of 15-90 µg is the dose delivered to the patient (as opposed to a quantity placed into a nebulizer or starting solution). EX2053, ¶55; EX2052, ¶65 n. 8.

c) Voswinckel JAHA

Voswinckel JAHA is a quarter-page abstract dated October 26, 2004 and titled "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension." EX1008. Voswinckel JAHA generally describes the delivery of inhaled treprostinil sodium to 17 patients with severe pulmonary hypertension using a "pulsed" Optineb® ultrasound nebulizer in three breaths, with a pre-aerosolized treprostinil solution of 600 µg/ml. *Id.*

Petitioner does not contend that Voswinckel JAHA teaches a dosage of 15 micrograms to 90 micrograms. Instead, Petitioner relies on Voswinckel JAHA for teaching "a low number of breaths for the aerosolized delivery of treprostinil specifically for the treatment of pulmonary hypertension." *Id.* at 40. A POSA, reading Voswinckel JAHA, would not be able to determine the delivered dose in 1 to 3 breaths based on the disclosure of JAHA. EX2053, ¶52. The dosage delivered using an unknown pulsed nebulizer would depend on a number of factors including the amount of aerosol delivered per pulse, the number of pulses generated per breath, the shape of the mouthpiece or mask, and the breathing pattern of the patient. *Id.*

Accordingly, because none of the identified references in Ground 1 teach a single event dosage of 15 micrograms to 90 micrograms or provide any motivation for administering this amount, this ground must fail even if all of the references are prior art (which they are not).

3. The POSA Would Not Be Motivated To Combine The '212 Patent, Voswinckel JESC, and Voswinckel JAHA With A Reasonable Expectation of Success

Petitioner concedes that neither the '212 patent nor Voswinckel JESC teach a single event dose of 15 micrograms to 90 micrograms in 1 to 3 breaths. Instead, Petitioner incorrectly argues that these two references render this limitation obvious based on three erroneous calculations. The first erroneous calculation relies on an undated Optineb manual, which Petitioner suggests provides a nebulization rate for an OptiNeb® ultrasound nebulizer. Yet there is no evidence that this manual is prior art or refers to a device that was available, much less used, in the reported studies. Petitioner incorrectly relies on this assumption to argue that the patients described in Voswinckel JESC may have received more than 1 ml of solution and leaps to conclude that these subjects received dosages of treprostinil within the claimed ranges.

The second erroneous calculation relies on unsupported assumptions provided by the testimony of Drs. Hill and Gonda that nebulizers are usually prescribed to deliver more than 1 ml of solution. Moreover, Dr. Hill relies on his experience as an investigator in the Tyvaso® clinical trials and approved drug label – the drug embodying disclosure of the '793 patent. EX2055, 96:3-101:12. Petitioner incorrectly relies on these unsupported assumptions to argue that the patients

described in Voswinckel JESC received more than 1 ml of solution and further received dosages of treprostinil within the claimed ranges.

The third erroneous calculation relies on the teaching in the '212 patent that "the actual amount of UT-15 delivered via aerosolization delivery is only a fraction (10-50%) of the dosage delivered intravascularly." EX1006, 8:8-12, *see* Pet., 38-39. Petitioner and Dr. Hill provide calculations of an inhaled dose based on this 10-50% fraction and the dosing calculations approved by the FDA for intravascular treatment with treprostinil. But as Dr. Hill acknowledged, it is misleading to compare blood levels during infusion as compared to after inhalation and not an accurate measure of the relative potency of treprostinil in aerosolization versus intravascular administration. EX2055, 102:13-104:15.

As discussed in detail below, each of these erroneous calculations is unsupported by the record.

a) Petitioner Fails to Establish That the Undated Optineb Manual or Optineb Device Was Publicly Available at the Priority Date

As a preliminary matter, while agreeing that Petitioner has not established that the undated Optineb manual is prior art (Institution Decision at 23), the Institution Decision relied on the undated Optineb manual "as evidence of the general knowledge in the art at around the time of the invention." *Id.* at 24 (citing *Koninklijke Philips N.V. v. Google LLC,* 948 F.3d 1330, 1337-1338 (Fed. Cir.

2020)). But even on this basis, Petitioner fails to show that the information disclosed in the undated Optineb manual was general knowledge as of the priority date.

The undated Optineb manual appears to be a translation of an Operating Instruction manual for "Optineb®-ir", a microprocessor-controlled, mobile ultrasonic nebulizer (Model No. ON-100/2-2.4 MHz). EX1037. This undated Optineb manual discloses certain technical features, including that the nebulizer output (what Petitioner's expert, Dr. Hill refers to as "nebulizing rate") is provided as 0.6 mL/min. *Id*. at 28. Petitioner relies on this technical detail to argue that Voswinckel JESC teaches "an effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil."

Dr. Hill first notes that Voswinckel JESC teaches "[d]oses of treprostinil in solution . . . of 16, 32, 48, and 64 µg/mL using an OptiNeb® ultrasound nebulizer." EX1002, ¶64. Dr. Hill next argues, without evidence, that nebulizers at the time were known to nebulize at least 1 mL by citing his personal experience and Petitioner's other expert, Dr. Gonda.[8] *Id.* at ¶65. As an initial matter, Dr. Hill

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[8] But Dr. Hill admitted that he did not recall reviewing Dr. Gonda's declaration prior to signing his own declaration that cites to Dr. Gonda's declaration; rather he relied on his attorneys' "verbal" explanations "relay[ing] the content to [him]." EX2055, 132:20-134:5.

testified that his personal experience was based drugs for other indications, not prostcyclins for the treatment of pulmonary hypertension. EX2055, 146:16-23. Dr. Gonda cites three drug labels, but only one involved a pulmonary hypertension treatment and none of the cited drugs used an OptiNeb device. Dr. Hill further argues that "[a] POSA would further confirm that 16-64 μg was the administered dosage in Voswinckel JESC by using his understanding of the rate of solution delivery for OptiNeb® device available before 2006." *Id.* at ¶67. Citing only the undated Optineb manual for the proposition that the nebulizing rate of Voswinckel JESC would be 0.6 mL/min, Dr. Hill argues that continuous delivery of inhaled treprostinil across 6 minutes as described in Voswinckel JESC would have resulted in a dosage of 57.6 μg (16 μg/mL * 0.6 mL/min * 6 min). *Id.*

Dr. Hill's analysis of Voswinckel JESC in view of the undated Optineb manual fails based on several unsupported assumptions.

First, neither Petitioner nor Dr. Hill provide any evidence for their assertion that the undated Optineb manual was publicly available before 2006. The undated Optineb manual does not provide any copyright information that would indicate when it was first published. Nor does Petitioner make any effort to fulfill its burden to demonstrate public accessibility before 2006. Indeed, Petitioner provides no indication that the Optineb manual was disseminated or publicly available and indexed in a manner substantiating public accessibility since there is no evidence

that it could be located before the critical date using key words. *Blue Calypso*, 815 F.3d at 1349; *see also In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989)." Dr. Hill merely assumed that the undated Optineb manual was available before 2006 and testified that the only basis for his conclusion that this document was available in 2005 was "from the attorneys." He did not "know where the derivation was beyond that." EX2055, 63:3-64:2, 83:8-22. Further, Petitioner retained an expert to authenticate the publication date of other documents, but that declaration is completely silent on EX1037. *See* EX1036. Regardless, the inventors of the '793 patent, who contributed to development of Optineb, have confirmed it was not available before the 2006. EX2003, ¶26; EX2071 (IPR2017-01621, EX2098) (Seeger Decl.), ¶14 (citing EX2101-EX2102). In sum, Petitioner has failed to make *any* evidentiary showing that Exhibit 1037, the undated Optineb manual was publicly accessible as of the critical date of the '793 patent.

Second, there is no evidence that the Optineb manual reflects "general knowledge in the art at around the time of the invention." Institution Decision at 24. The Optineb manual is not being used for general knowledge, such as the existence of nebulizers capable of delivering drug within the recited parameters. Dr. Hill specifically used the Optineb manual to determine "the rate of solution delivery for the OptiNeb® device available before 2006," *i.e.*, the deliver rate of a prior art device. EX1002, ¶67. Dr. Hill confirmed that in addition to relying on EX1037 in

forming his opinion, he had no personal basis for his conclusion that this document was available in 2005, stating only that he "got it from the attorneys." EX2055, 63:3-64:2. He further testified that as of 2006 he had never used an OptiNeb device and that he had not tried to verify whether EX1037 came from the 2005. *Id.* Nonetheless, Dr. Hill relies on the Optineb manual for a specific fact integral to his calculations: an alleged nebulizing rate of 0.6 mL/min. There is no evidence that 0.6 mL/min or even a similar nebulization rate was general knowledge at the time of invention, suggesting reliance on hindsight.

Third, Dr. Hill assumes without evidence that the "OptiNeb ultrasound nebulizer, Nebu-tec, Germany" is *the same Optineb device* described in the undated Optineb manual. However, Dr. Hill conceded that he did not know what the "IR" refers to or whether the various Optineb models are the same or different devices. EX2055, 61:10-62:25. In fact, Dr. Hill did not know whether the Optineb device of EX1037 was the same device used in Voswinckel JESC because the reference does not identify which model was used. *Id.* at 81:12-22; 83:3-7.

Further, while the undated Optineb manual states the nebulizer output is 0.6 ml/min (EX1037, 28), that number is far too unsubstantiated and unclear to support any conclusions about actual nebulizer output in any specific instance. EX2053, ¶81. For example, the manual states that this particular nebulizer model has six different programs or modes (EX1037 at 18-20). In certain modes (P1, P2, and P3),

the device generates aerosol at intermittent intervals, while in other modes, it generates aerosol continuously. *Id.* Moreover, EX1037 fails to explain whether the 0.6 number is a maximum, minimum, or average; whether the number is a theoretical output based on the electrical components in the nebulizer or the ultrasonic horn driving nebulization of the aerosol; or, if the 0.6 ml/min was derived empirically, whether the measurements were of nebulization of pure water, or a solvent, or a mix of both, or if there was a drug or placebo in the solution. EX2053, ¶¶81-83. All of these variables could affect the amount of drug in the nebulizer output. *Id.*

As a result, even if the Optineb device disclosed in Voswinckel JESC were the same nebulizer described in the undated Optineb manual, there are too many unknowns such that a POSA could not calculate a single event dose. For example, Voswinckel JESC does not describe which program, face mask or mouthpiece, type of tubing, operation frequency, or which baffle plate was used, and all of these variations can effect the device's output. EX2053, ¶¶75-83. Thus, a POSA would not have been able to determine the dosage delivered in Voswinckel JESC with any reasonable certainty.

Because all of the factors addressed above affect the amount of aerosolized treprostinil delivered to the patient and are thus necessary factual predicates for Petitioner's statement that Voswinckel JESC teaches the claim element "wherein the therapeutically effective single event dose comprises from 15 micrograms to 90

micrograms of treprostinil or a pharmaceutically acceptable salt thereof," Grounds 1 and 2, which rely only upon Voswinckel JESC when read in view of the undated Optineb manual to supply this limitation, must fail.

b) Petitioner Fails to Establish That Fill Volume is Sufficient to Determine the Single Event Dose

With respect to Voswinckel JESC, Petitioner's argument that "a POSA would have expected at least 1 mL of the treprostinil solution was used over 6 minutes of inhalation, and thus would understand, therefore, at least 16, 32, 48, or 64 μg of treprostinil were delivered to different dosing groups in this study" (*see* Petition at 23, EX1002, ¶99; EX1004, ¶56) is flawed on several grounds.

First, the single event dose of treprostinil delivered to a patient using a continuous nebulizer cannot be meaningfully determined using only the fill volume (*i.e.* the amount of pre-aerosolized solution loaded into the nebulizer). In practice, patients may be administered an inhaled therapeutic through a continuous nebulizer until the solution in the reservoir has been completely nebulized. *See* EX2052, ¶83. For example, each of the FDA approved labels, which Dr. Gonda cites to in his declaration, involve administering the solution until the contents of the reservoir of the nebulizer are emptied. EX.1004, 56, n. 4. But Voswinckel JESC does not describe nebulization until the reservoir is emptied. It mentions a six-minute time period, and there is no guarantee that the entire fill volume would be completely nebulized in six minutes. EX2052, ¶83; EX2053, ¶45.

The labels Dr. Gonda relies on indicate wide variability in the time required to nebulizer all of the solution. For example, the AccuNeb® Label referred to by Dr. Gonda teaches that it may take anywhere from 5 to 15 minutes for the 3 mL solution to be nebulized.[9] EX.1004, 56, n. 4; EX1066. Voswinckel JESC does not provide either the starting volume of treprostinil solution or identify whether the entire volume had been nebulized at 6 minutes. The AccuNeb® label also explicitly recognizes that *delivery* of a dose to the patient – as opposed to what is converted to an aerosol by nebulization – depends not only the nebulizer itself, but also on patient factors. EX2053, ¶61.

Second, even if Voswinckel JESC taught a starting volume of solution with a specified concentration of treprostinil, and further taught that the solution was completely nebulized – which Voswinckel JESC does not – a POSA still would not be able determine the single event dosage over that six-minute interval without additional information about the nebulization device. Fill volume is just one of many variables that may affect drug dosage. EX2001, ¶41; EX2053, ¶¶55-56. Additional factors that may affect the dose of drug received by a patient through a continuous

[9] Dr. Hill admitted that AccuNeb® is not used to treat pulmonary hypertension and there may be different considerations in determining whether a particular medication is suitable via a particular mode of administration. EX2055, 136:8-141:18.

nebulizer include gas flow and pressure, fill and dead volumes, gas density, and humidity and temperature conditions, breathing pattern, and device interface. *See, e.g.,* EX2033, 11-12; EX2001, ¶13; EX2053, ¶55-56. These factors are not uniform between nebulization devices or patients; EX2053, ¶61. Thus, without additional information regarding the numerous factors mentioned above, the single event dose delivered to patients in Voswinckel JESC cannot be determined. EX2053, ¶¶55-60, 68.

Third, it is not true that all continuous nebulizers deliver a dosage of between 1 and 5 mL of aerosolized solution. *See, e.g.,* EX2082, 13; EX2053, ¶¶69-73. Certain commercially available nebulizers –available as of the priority date – were suitable for use with at least 0.5 mLs. *See, e.g.,* EX2082; EX2053, ¶71. Other nebulizers were known to deliver more than 5 mL of aerosolized solution. *See, e.g.,* EX2053, ¶71. A POSA would not know one way or the other whether the ultrasonic Optineb device of Voswinckel JESC was filled with more than 1 mL or less than 5 mL of solution. EX2053, ¶72.

Finally, as discussed in Section IV.A.2.a), it is impossible to extrapolate what an appropriate single event dose should be from the data included in Voswinckel JESC because the delivery efficiencies and pharmacokinetics of a continuous nebulizer to do not predictably translate to devices capable of delivering consistent

dosages in just 1 to 3 breaths. *See, e.g.*, EX2061, ¶¶11, 14-15 (citing IPR2017-01622, EX2049, EX2050, EX2051).

c) Petitioner's Calculation of Dose Based on the Teachings of the '212 Patent are Flawed For Several Reasons.

Alternatively, Petitioner starts from the premise that the '212 patent "discloses a dosage range for intravascular administration of treprostinil for the treatment of pulmonary vascular disease, and discloses that only 10-50% of the dosage delivered intravascularly would be needed via inhalation *to have the same therapeutic effect*." *See, e.g.,* Petition at 30-31, 38-39. Petitioner's incorrect calculation starts with the fact that intravascular treprostinil is approved to treat pulmonary hypertension at a dosage of 1.25 ng/kg/min. Petitioner then calculates that a patient weighing between 60 and 65 kg would receive a dosage of 108 to 117 micrograms per day. Petitioner argues that a POSA would then "apply the '212 Patent's 10-50% adjustment between intravascular and inhaled dosing to achieve a dosage of 10.8 to 58.5 micrograms." This analysis is flawed, because (i) the '212 patent does not provide a mathematical calculation for converting an intravascular dosage to an inhaled dosage; and (ii) Petitioner's flawed calculation establishes a *daily* dose not a *single event* dose.

What the '212 patent actually teaches is that "aerosolized [treprostinil] has a *greater potency* as compared to intravascularly administered [treprostinil]." EX1006, 8:8-10 (emphasis added). The '212 patent further explains, "the actual

amount of [treprostinil] delivered via aerosolization delivery is only a fraction (10-50%) of the dosage delivered intravascularly." *Id.* at 8:10-13. However, the '212 patent notes that "the mechanism(s) that accounts for the greater potency and efficacy for aerosolized UT-15 is unknown." *Id.* at 8:13-15.

Petitioner improperly reads into this disclosure a mathematical formula for converting a therapeutically effective dose of intravascularly administered treprostinil into a therapeutically effective dose of inhaled treprostinil. But the '212 patent provides no such formula. The '212 patent simply notes that inhaled solutions are more potent despite the fact that the delivered dose may only be 10-50% of the aerosolized solution. Nor do the examples support such a calculation. The examples described in the '212 patent simply demonstrate that at the *same dosage* (250, 500 and 1000 ng/kg/min) and *same duration* (30 and 60 minutes), UT-15 is more potent in aerosolized form than intravenous form. *See* EX1006, 11:7-13. There is nothing in this data to suggest a formula for calculating the therapeutic dosage of inhaled treprostinil from an approved intravascular treprostinil treatment.

Further, Petitioner's oversimplified calculation fails to take into account the difference in pharmacokinetic effects of a large dose of treprostinil delivered in 1-3 breaths. Large doses of treprostinil were known to produce "dose-limiting side effects" such as nausea, vomiting, headache, dizziness, and anxiety. *See, e.g.,* EX2037. For subcutaneous administration, the maximal tolerated dose is just 10

ng/kg/min, which is 2 orders of magnitude lower than the claimed dosage of the '793 patent. *Id.* As discussed above, intravascular treprostinil is approved at a much lower dosage of 1.25 ng/kg/min. EX1018.

Dr. Hill admits that it "is misleading to rely on blood levels, circulating levels" and "rough measures of relative potency between intravascular and aerosolized delivery." EX2055, 103:21-104:6; *see also* EX2090, 460. And Dr. Hill, outside of this IPR proceeding, would never rely upon the calculation he puts forward here. In his own publications, including one 8 years after the priority date, when not being paid by Liquidia to say the opposite, Dr. Hill told his colleagues that "how the pharmacokinetics and the effectiveness of inhaled forms compare to parental forms [i.e. intravenous and subcutaneous] of prostanoids at the currently approved doses . . . has not been adequately studied." EX2090, 460; *see also* EX2061, ¶11 (noting risk of spillover effect when inhaled amount of treprostinil is increased). Instead, "clinicians need to rely on clinical assessment as proof of response to therapy." *Id.*

Iloprost, the only other inhaled prostacyclin analogue as of the priority date, approved for dosages of 5 micrograms or less in a single event dose, demonstrated adverse systemic effects at doses as low as 7.5 micrograms per single event dosage. EX1001, 17:15-22. Given these dose limiting side effects, a POSA would not have been motivated to achieve a dose of 15 to 90 micrograms in just 1 to 3 breaths with any reasonable expectation of success.

Finally, even if the Board were to accept Petitioner's calculation, it does not result in a single event dose between 15 micrograms and 90 micrograms. Remodulin® intravenous infusion is dosed *continuously*, and 108 to 117 micrograms would be the dosage over *24 hours*. *Id.*, EX1018. The '212 patent teaches, therefore, that 10.8 to 58.5 micrograms would be the expected *daily* inhaled dose, and not a single event dosage. *Id.* As Dr. Hill admits, this calculation is comparing "apples and oranges." EX2055, 100:15-25.

The continuous nature of the drug delivery in the prior art confirms that one single event dose is insufficient to control PAH for an entire day. *Id.* For example, Voswinckel JAHA, which has itself not been established to be prior art, confirms that 4 individual dosing events were required throughout the day to treat pulmonary hypertension. *Id*; EX1008. Even at the high end, the simple math demonstrates that a 58.5 microgram daily dose would amount to less than 15 micrograms of treprostinil sodium per single event dose when spread over four individual dosing events. *Id.*

Surprisingly, during Dr. Hill's deposition, Petitioner asked about "dose adjustments" of Remodulin as described on the label on redirect. Dr. Hill testified that the dose of Remodulin may be adjusted "no more than 2.5 nanograms per kilogram per minute per week". *Id.* at 174:15-21. Dr. Hill then testified that these dose adjustments would "end up in that 15 to 90 microgram range taking into account dividing the dose in paragraph 100 by four." *Id.* at 176:5-10. Patent Owner

objects to this testimony because it is outside the scope of a proper redirect examination and presents new theories of invalidity that were not presented in the Petition. Further, following the dosage instructions from the Remodulin label would ultimately result in dosages significantly above a single event dose of 15 to 90 micrograms even if Petitioner's calculation methodology had any scientific merit, which it does not. *See, e.g.,* EX2052, ¶60.

For at least these reasons, a POSA would not be motivated to combine the disclosure of the '212 patent with the teachings of Voswinckel JESC and JAHA in a way that would result in a single event dose of 15 to 90 micrograms in 1 to 3 breaths with a reasonable expectation of success. There is simply no motivation offered by Petitioner that would override a POSA's serious concerns about side effects to support modifying the Voswinckel references and '212 patent in order to achieve a single event dose of 15 to 90 micrograms in 1 to 3 breaths. In fact, Voswinckel JESC warns in its Conclusion that "at a concentration of 16 μg/ml, near maximal pulmonary vasodilation is achieved without adverse effects" but "[a]t higher doses, local and systemic side effects may occur." EX1007. Nowhere does the Petition address why a POSA would increase the dose or have a reasonable expectation of success if the dose is increased by shortening the single event dose of Voswinckel JESC to 1 to 3 breaths using a much higher dose per breath. In fact, Petitioner's expert Dr. Gonda remarks in his own inhaled treprostinil patent

application that it would be preferable to *reduce* the treprostinil dosage taught by Voswinckel 2006 in order to reduce systemic levels and adverse side effects. EX2091, ¶¶25, 26, 29-32. If anything, a POSA would be motivated to lower the dose based on Voswinckel 2006 (if it were prior art at all).

4. Claims 4, 6, and 7: Petitioner's Arguments Regarding Obviousness Are Contradicted And Undermined By Its Arguments Regarding Enablement

Here, Petitioner asserts that claims 4, 6, and 7 are obvious. But in co-pending litigation between Petitioner and Patent Owner, Petitioner says the claims are not enabled. Petitioner cannot have it both ways.

Petitioner uses half of a page to assert that claim 4 would be obvious. Pet. 44. Petitioner cites the '212 patent, which describes an "inhaler" and references powder formulations in the specification and a claim, and an article stating that "dry powder inhalers were well known and 'widely accepted' as of 2006." *Id.* (citing EX1038, 1311). Petitioner cites the'212 patent again for claims 6-7, using four and three lines, respectively. Pet. 45. Dr. Gonda's declaration asserts that "because dry powder inhalers were well-known and 'widely accepted' by May 2006, … a POSA would have had a reasonable expectation of success that the "powder" disclosed and claimed in the '212 Patent could be 'inhaled' by a patient using a dry powder inhaler." EX1004, ¶80 (citing EX1019, 33).

Dr. Gonda asserts the opposite in his district court expert report. Spanning twenty pages, Dr. Gonda identifies a litany of alleged challenges that he contends demonstrate a lack of enablement.[10] EX2091, 40-61. According to Dr. Gonda, "a POSA would have to engage in excessive (undue) experimentation to develop a treprostinil powder formulation and corresponding dry powder inhaler that achieve [sic] effective administration as required by claims 1, 4, 6, and 7 of the '793 patent." *Id.* at 42. "[T]he level of unpredictability in the art was high." *Id.* at 44. "Without guidance from the '793 Patent, ***a POSA would be unable*** to formulate a treprostinil powder suitable for administration via a dry powder inhaler for PH patients without excessive experimentation." *Id.* at 47 (emphasis added); *see also, e.g.*, *id.* at 49 (treprostinil would be more challenging that other drugs used with DPIs); 51 (powders present unique challenges).

Dr. Gonda's opinions in the district court completely contradict his assertions before the Board. *Compare* EX2091, 40-61 *with* Pet. 44 *and* EX1004, ¶¶76-80. This is particularly true where Petitioner and Dr. Gonda contend that "the '212 patent's disclosure that one can use a powder formulation of treprostinil is nearly identical to that of the '793 patent's disclosure of treprostinil powder formulations." EX1004,

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[10] Patent Owner disputes Petitioner's claims of invalidity for lack of written description and enablement and obviousness.

¶78 n.8. "[N]early identical" disclosures cannot support both a reasonable expectation of success (*without* the '793 patent's guidance on dosing) and a conclusion of undue experimentation (*with* the '793 patent's guidance).

Dr. Gonda purports to condition his opinions on enablement, stating that the claims are not enabled "[t]o the extent [Petitioner] contends that he asserted claims are not obvious," but this does not resolve his inconsistency. *See, e.g.*, EX2091, 40. Patent Owner primarily contends the claims are nonobvious because the prior art lacks disclosure of a single event dose of 15-90 μg delivered in 1-3 breaths, regardless of the form of administration (liquid or powder). Whether the Board or Court agrees does not affect how difficult it allegedly was in 2006 to prepare a powder formulation for use with a DPI. Petitioner's conclusory evidence of obviousness is contradicted by its lengthy district court assertions and it has therefore failed to show Claims 4, 6, or 7 to be obvious by a preponderance of the evidence.

B. Ground 2: the '212 Patent and Voswinckel JESC Fail to Render Claims 1-8 Obvious

Petitioner's rationale under Ground 2 is identical to Ground 1, except with respect to the claim limitation "delivered in 1 to 3 breaths." Rather than relying on Voswinckel JAHA for this limitation, Petitioner argues that this limitation "would have been obvious over the '212 Patent and Voswinckel JESC in view of a POSA's general knowledge in the field and/or by applying routine optimization." To the

extent that Ground 2 relies on arguments set forth under Ground 1, Patent Owner incorporates the arguments from Section IV.A.

Petitioner is incorrect that a "POSA's general knowledge in the field" would motivate a POSA to "minimize the number of breaths required for administration of treprostinil." As discussed above, there were known dose limiting side effects associated with treprostinil and prostacyclin molecules generally that would have prevented a POSA from expecting that such a high dosage in just 1 to 3 breaths would be well tolerated. *See* Section IV.A.3.c). The "general knowledge" relied upon by Petitioner does not support the notion that the "the general state of the art had established safety and efficacy of high dosages of inhaled therapeutics delivered over a small number of breaths."

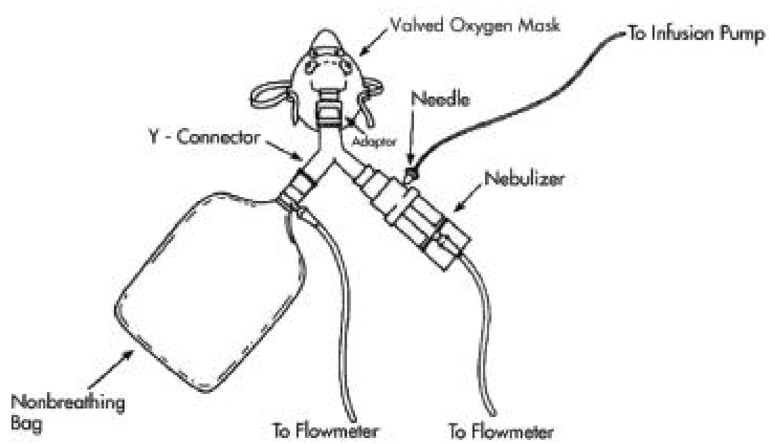
As a preliminary matter, Petitioner relies on publications that are not "prior art" as discussed in Section IV.C below (*i.e.*, Voswinckel 2006 (EX1009) and Ghofrani (EX1010)).

Second, even the actual prior art relied upon relate to different types of molecules with different indications and mechanisms of action. Geller 2003, for example, which Petitioner also relies upon, teaches inhalation of recombinant human deoxyribonuclease (rhDNase) for the treatment of cystic fibrosis. EX1034, Abstract. A POSA would understand that the ability of an inhaled therapeutic to be well tolerated at high concentrations in just 1 to 3 breaths is highly dependent on the

nature of the compound inhaled. EX2052, ¶89. The pharmacokinetic profile and potential side effects of inhaled rhDNase are completely unrelated to treprostinil or other prostacyclin analogues. *Id*. And Frijlink 2004 (EX1039) simply teaches that dry powder inhalers may be used to deliver high fine particle fractions to the lung resulting in relatively high lung deposition. It does not teach that high concentrations of treprostinil in just 1 to 3 breaths would be well tolerated in the case of a totally different patient population, namely pulmonary hypertension patients. Indeed, Dr. Hill acknowledged that there are different considerations in determining whether a particular medication is suitable via a particular mode of administration when treating different diseases. EX2055, 136:8-141:18. Finally, Petitioner relies upon Voswinckel JAHA, but as explained in Section IV.A.2.c) above, this abstract does not teach dosages of treprostinil of 15 micrograms to 90 micrograms.

Petitioner has likewise failed to explain *why* it would have been "routine optimization" to arrive at the claimed dosage in just 1 to 3 breaths in view of the general disclosures of the '212 patent and Voswinckel JESC. As discussed in Sections IV.A.2.a) and IV.A.2.b) above, neither the '212 patent nor Voswinckel JESC teach a single event dose of 15 micrograms to 90 micrograms or teach administration of treprostinil in just 1 to 3 breaths. In fact, Voswinckel JESC teaches away from using higher concentrations due to side effects as described above.

Petitioner incorrectly assumes that a POSA could readily titrate dosage up from the teachings of the ’212 patent and Voswinckel JESC to achieve a single event dose of 15 micrograms to 90 micrograms in 1 to 3 breaths. However, both the ’212 patent and Voswinckel JESC utilize continuous nebulization to deliver a dosage of treprostinil over a longer duration. It would not be possible to administer a single event dose in 1 to 3 breaths of the claimed invention using these devices. Further, as discussed *supra*, with continuous nebulization, a patient breathes in a very small fraction of the nebulized output of the device over a substantial time period without knowing the precise dosage that is ultimately administered. *Id.* (“only 10% of the total dose loaded in a [continuous] nebulizer is in reality deposited in the lungs”). The patient wears a mask and breathes in unmeasured portions of the entire nebulized output delivered through the mask:



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EX2033, EX2052, ¶37.

Various factors that would affect the dose of drug received by a patient through a continuous nebulizer include gas flow and pressure, fill and dead volumes, gas density, and humidity and temperature conditions, breathing pattern and device interface. *Id.* at ¶38. Petitioner overlooks the fundamental difference between operating principles of continuous nebulization devices and other types of inhalation devices and erroneously combines elements from incompatible references throughout its Petition.

Petitioner's assertions of obviousness of claims 4, 6, and 7 fail for the same reasons as cited above with respect to Ground 1.

C. Grounds 3-6 Fail Because Each Ground Relies On Publications That Petitioner Has Failed to Establish Are Prior Art

Petitioner does not dispute that Ghofrani and Voswinckel 2006 were both published less than one year prior to the date of the application that resulted in the '793 patent. *See, e.g.,* Petition at 25 (admitting that Ghofrani was published in June of 2005, *i.e.*, less than one year prior to the date of application); *Id.* at 27 (admitting that Voswinckel 2006 was published on January 17, 2006, *i.e.*, less than one year prior to the date of application). Accordingly, Petitioner bears the burden of establishing that Ghofrani and Voswinckel 2006 are prior art "by others" under 35 U.S.C. § 102(a). *See, e.g., Lacks Industries, Inc. v. McKechnie Vehicle Components USA, Inc.* 322 F.3d 1335, 1346 (Fed. Cir. 2003) (an inventor's own disclosure 'will

not anticipate his later invention" unless published more than one year prior to the application date).

Ghofrani and Voswinckel 2006 are not prior art unless they are the work of another. *In re Katz,* 687 F.2d 450, 454 (CCPA 1982). "[T]he fact that a reference does not list any co-inventors as authors, or that it lists other authors, is certainly not dispositive in itself." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014); MPEP § 2132.01 (II) ("[a]n inventor's or at least one joint inventor's disclosure of his or her own work within the year before the application filing date cannot be used against the application as prior art under pre-AIA 35 U.S.C. 102(a)."). A common inventive entity may still exist even where a co-inventor is not listed as an author on the purported prior art reference. *See, e.g., Trans Ova Genetics, LC v. XY, LLC,* IPR2018-00250, paper 35, at 7-8, n. 8 (PTAB Jun. 26, 2019). The relevant inquiry is whether the co-authors that are not listed as inventors on the '793 patent invented the portions of the reference relied upon as prior art. *Cellco Partnership v. Bridge and Post, Inc.*, IPR2018-00054, paper 40, 20 (PTAB Apr. 15, 2019) (citing *In re Land,* 368 F.2d 866, 878 (CCPA 1996) and *In re DeBaun*, 687 F.2d 459, 462-63 (CCPA 1982)).

The declarations of inventors Drs. Seeger and Roscigno, together with the deposition testimony of Dr. Rubin and the corroboration provided by non-inventor Dr. Ghofrani, establish that the relevant portion of the Ghofrani reference was

reduced to practice by the present inventors prior to the publication date of the Ghofrani reference. EX2071, ¶5; EX2074, ¶8. In addition, Dr. Roscigno confirms and identifies corroborating regulatory documents demonstrating that the inventors had conceived of and reduced to practice all limitations of the independent claims by 2003, and certainly no later than January 2005. EX2061, ¶¶16-17 (citing EX2062-EX2064). Certainly, the inventors had reduced to practice at least the limitations alleged in Ghofrani by the end of 2003 and no later than January 2005. *Id.* at ¶14-15. The same is true in relation to Voswinckel 2006. Accordingly, Ghofrani and Voswinckel 2006 are not qualifying prior art.

1. Ghofrani

Ghofrani is a review article, published in German, describing "New therapies in the treatment of pulmonary hypertension." In addition to describing recent developments relating to inhaled treprostinil, the review article also describes other "new therapy approaches, which are partially still under development, and that can find their way into the therapy guidelines in the near future" including inhaled iloprost, selective endothelin A receptor antagonists (sitaxsentan and ambrisentan), and PDE5-inhibors (e.g., sildenafil). EX1010, 297.

The Ghofrani review article was co-authored by Drs. Seeger and Voswinckel (inventors of the '793 patent) as well as Drs. Ghofrani, Reichenberger, and Grimminger (non-inventors). Drs. Seeger and Voswinckel testified that they

contributed to portions of the Ghofrani review article relating to inhaled iloprost and inhaled treprostinnil. *See* EX2066, 3 (IPR2017-01621, EX2020) (Seeger Decl.). Drs. Ghofrani, Reichenberger, and Grimminger have each submitted declarations stating that they did not contribute to the sections of the Ghofrani review article relating to the studies on inhaled treprostinil. EX2004, ¶ 5; EX2005, ¶ 5; EX2006, ¶ 5; *see also* EX2067-EX2069 (IPR2017-01621 and -01622) (Ghofrani, Grimminger, Reichenberg Decls.) (EX2026, EX2099, EX2028, EX2027). Further, Drs. Ghofrani, Reichenberger, and Grimminger have each declared that they did not design the inhaled treprostinil clinical trials and that the information on the clinical trials mentioned in the Ghofrani article were designed and conducted by Drs. Voswinckel and Seeger based on their work with Drs. Olschewski, Rubin, Schmehl, Sterritt, and Roscigno. *Id.*

Instead, Drs. Ghofrani, Reichenberger, and Grimminger contributed to other sections of Ghofrani not relevant to the Petitioner's grounds for *inter partes* review. Dr. Ghofrani stated that his contribution was to the section on phosphodiesterase inhibitors. EX2004, ¶4. Dr. Ghofrani has experience in the use of phosphodiesterase inhibitors for treatment of pulmonary hypertension. *Id.* His contribution to the Ghofrani publication was drafting the section of the article relating to phosphodiesterase inhibitors and jointly drafting the sections on vasoactive therapy, inhaled iloprost, combination therapies, and treatment of early forms of treatment of

pulmonary hypertension, as well as the introduction. *Id.* His work was limited to these sections, and he did not contribute to the portion of Ghofrani relied upon by Liquidia. *Id*. at ¶¶4-6.

Dr. Reichenberger stated that his contribution was to the section on selective endothelin A receptor antagonists. EX2005, ¶4. Dr. Reichenberger has experience in the use of selective endothelin A receptor agonists for treating pulmonary hypertension. *Id*. His contribution to Ghofrani was jointly drafting the section on selective endothelin A receptor agonists with Dr. Grimminger. *Id.* His work was limited to these sections, and he did not contribute to the portion of Ghofrani relied upon by Liquidia. *Id*. at ¶¶4-6.

Dr. Grimminger stated that his contribution was also to the section on selective endothelin A receptor antagonists. EX2006, ¶4. Dr. Grimminger has experience in the use of selective endothelin A receptor agonists for treating pulmonary hypertension. *Id*. His contribution to Ghofrani consisted of jointly drafting the section on selective endothelin A receptor agonists with Dr. Reichenberger. *Id.* His work was limited to these sections, and he did not contribute to the portion of Ghofrani relied upon by Petitioner. *Id.* at ¶¶4-6.

As noted in *In re Katz*, "authorship of an article by itself does not raise a presumption of inventorship with respect to the subject matter disclosed in the article. Thus, co-authors may not be presumed to be co-inventors merely from the

fact of co-authorship." 687 F.2d at 455. The explanations provided by Seeger and *each of the non-inventor co-authors* – Drs. Seeger, Ghofrani, Reichenberger, and Grimminger – is consistent not only with the content of the article, but also with the nature of the publication, *i.e.*, a review article summarizing different advances in the treatment of pulmonary hypertension. *Id.* (accepting the Appellant's explanation "consistent not only with the content of the article but with the nature of the publication"). From such a fact pattern, joint inventorship with Drs. Ghofrani, Reichenberger, and Grimminger cannot be inferred.

Further, Petitioner appears to accept UTC's explanation for why Drs. Ghofrani, Reichenberger, and Grimminger are not inventors of the relevant subject matter of Ghofrani based on declarations submitted by these authors in IPR2017-01621. *See,* Pet. at 26 ("PO encountered this issue in IPR2017-01621 and IPR2017-01622 and submitted an affidavit attesting that these authors did not contribute to the relevant portion of Ghofrani. *See* IPR2017-01621; Paper 10 at 12-14; IPR2017-01622, Paper 9 at 12-15.")

Nonetheless, Petitioner contends that because "Olschewski, Rubin, Schmehl, Sterritt, and Roscigno were not listed as authors on the Ghofrani article"[11] there is an "inference that they did not make any contribution to Ghofrani's disclosure." *Id.* at 27. This distinction between authorship and inventorship is legally irrelevant. The fact that a reference does not list certain co-inventors as authors is not dispositive on the issue of whether a prior art reference is the work of another. *See, e.g., Allergan, Inc. v. Apotex Inc.*, 754 F.3d at 969. There is no requirement that every listed inventor on the '793 patent be listed as a co-author to disqualify a reference under § 102(a) as not by another. *See, e.g., Trans Ova Genetics, LC v. XY, LLC,* IPR2018-00250, Paper 35 at 7-8, n. 8. The relevant inquiry is whether the co-authors that are not listed as inventors on the '793 patent invented the portions of the reference relied upon as prior art. *See, e.g.*, *Cellco Partnership v. Bridge and Post, Inc.*, IPR2018-00054, Paper 40 at 20.

Here, the declaration of Dr. Seeger explains that these other co-inventors helped design the development program for the claimed invention of the '793 patent including designing the pilot and pivotal trials, which resulted in three clinical

[11] Robert Roscigno is a named inventor of the '793 patent, and was later employed as an executive of, and is currently a consultant for, Liquidia. Petitioner failed to present *any* evidence on these points.

studies that became the basis of the patent application leading to the ’793 patent. EX2003, ¶¶12, 22-27. Many of the specific parameters used in these studies performed by the co-inventors were not fully reported in Ghofrani. *Id.* at ¶¶11-12. In addition, Dr. Roscigno further confirms and corroborates that the clinical trials underlying the relevant portions of Ghofrani were conceived by the named inventors and not by the non-inventor co-authors of these references. EX2061, ¶¶12-17. Accordingly, the absence of these co-inventors as authors on the Ghofrani review article is irrelevant to whether Ghofrani is "by another."

2. Voswinckel 2006

Voswinckel 2006 is a short "Clinical Observation" published in the Annals of Internal Medicine, titled "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," which describes clinical observations on three patients with severe pulmonary hypertension, who were treated with administration of a single 15 μg dose of treprostinil, inhaled in three breaths through a modified Optineb ultrasonic inhalation device.

Voswinckel 2006 was co-authored by Drs. Seeger, Voswinckel, and Dr. Olschewski (inventors of the ’793 patent) as well as Drs. Ghofrani and Grimminger (non-inventors). Drs. Ghofrani and Grimminger have each submitted declarations stating that they did not contribute to design or control of the clinical trial described in Voswinckel 2006, and that all of the work performed by Drs. Ghofrani and/or

Grimminger was at the direction of or under the supervision and control of Drs. Seeger, Voswinckel, and Olschewski. EX2004, ¶¶7-12; EX2006, ¶¶7-12; *see also* EX2070, ¶6; EX2065. A publication is not the work of another where the work described was performed solely at the direction and supervision of the listed inventor(s). *See In re Katz,* 687 F.2d at 450, 455-456 (holding that a publication that identified an inventor and two students as authors was not the work of others, and thus not prior art, because the work performed by students in "testing features of the invention" was performed under the direction and supervision of the inventor); *see also CSL Behring LLC v. Bioverative Therapeutics Inc.,* IPR2018-01313, paper 10, 11 (PTAB Jan. 9, 2019) (holding a publication is not the work of another where the patent owner can show that the non-inventor co-authors "carried out experiments under [the inventor's] direction and control," and that it was the inventor who "designed and lead the … project, and experiments performed by the co-authors.").

As set forth in the declarations, the dosage amounts of administered inhaled treprostinil to give to patients, the inhalation time and/or number of breaths employed, the particular equipment and administration devices and methods to use, the spacing between inhalation events, the analysis of the hemodynamic and pharmacokinetic effects over time in the study with inhaled treprostinil were all determined Drs. Seeger, Voswinckel, and/or Olschewski. Drs. Ghofrani and Grimminger did not participate in the design of any of the studies, did not select the

dosing regimen, and did not conduct analysis of patient results discussed in Voswinckel 2006. EX2004, ¶¶11-12; EX2006, ¶¶11-12.

As explained in the declarations of Drs. Seeger, Ghofrani, and Grimminger, it was standard practice within the group to include *all* group members as authors on clinical observation reports such as Voswinckel 2006, even when that group is broader than the individuals actually involved in inventing the methods or devices and designing the trials disclosed in that publication. EX2003, ¶21; EX2004, ¶¶10-11; EX2006, ¶¶10-11. This explanation is consistent with industry practice for publishing clinical observation reports such as this one. Joint inventorship with Ghofrani and Grimminger cannot be inferred in these circumstances.

Petitioner contends that "Olschewski, Roscigno,[12] Rubin, Schmehl, and Sterritt are identified as inventors of the '793 patent, but are not authors of Voswinckel 2006." Pet., 29. As a preliminary matter, UTC notes that Dr. Olschewski is an author on Voswinckel 2006.

Petitioner is also incorrect to state that, because these other co-inventors "are not authors on Voswinckel 2006, [this] supports the inference that they did not make any contribution to that disclosure." Pet. at 29. As discussed above with respect to Ghofrani, this fact is legally irrelevant. The fact that a reference does not list certain

[12] *See* footnote 4, above.

co-inventors as authors is not dispositive on the issue of whether a prior art reference is the work of another. *See, e.g., Allergan, Inc. v. Apotex Inc.*, 754 F.3d at 969. Rather, as is the case here, the non-author co-inventors, contributed to aspects of one or more of the claimed inventions, not disclosed by the publication that Petitioner is relying on.

Here, Dr. Seeger explains that these co-inventors helped design the development program for the claimed invention of the '793 patent including designing the pilot and pivotal trials, which resulted in three clinical studies that became the basis of the patent application leading to the '793 patent. EX2003, ¶¶19-20, 22-27. Many of the specific parameters used and the particulars of these studies performed by the co-inventors were not fully reported in Voswinckel 2006 (for example, the particular details of the "*modified* OptiNeb® ultrasonic device"). *Id.* at ¶19. In addition, Dr. Roscigno further confirms and corroborates that the clinical trials underlying the relevant portions of Voswinckel 2006 were conceived by the named inventors and not by the non-inventor co-authors of these references. EX2061, ¶¶12-17. Accordingly, the absence of these co-inventors as authors on Voswinckel 2006 is not dispositive on the issue.

V. OBJECTIVE INDICIA OF NONOBVIOUSNESS

There are a number of secondary considerations that establish that the claims of the ’793 patent are not obvious as of the priority date, including unexpected results, copying and unmet need.

A. Unexpected Results

For the reasons discussed above, Petitioner has failed to establish a prima facie case of obviousness under any one of Grounds 1-6. Moreover, the specification teaches the claimed single event dose of “15 micrograms to 90 micrograms of treprostinil” “delivered in 1 to 3 breaths” unexpectedly achieved a therapeutically effective dose that was well tolerated which further supports non-obviousness of the claimed inventions. A claimed dosage regimen as claimed in the ’793 patent is non-obvious where it “produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.” *In re Aller*, 220 F.2d 240, 456 (CCPA 1955); *E.I. DuPont de Nemours & Company v. Synvina C.V.,* 904 F.3d 996, 1007 (Fed. Cir. 2018); *In re Geisler,* 116 F.3d 1465, 1471 (Fed. Cir. 1997). Further, said critical range may be non-obvious, where the prior art taught away from the claimed range. *Ormco Corp. v. Align Technology, Inc*, 463 F.3d 1299, 1311 (Fed. Cir. 2006). Here, high doses of treprostinil were known in the art to produce dose-limiting side effects. As a result, a POSA would not have expected such dosage ranges delivered in just a few breaths to be well tolerated. EX2061, ¶¶11, 14-16

(citing IPR2017-01622, EX2049, EX2050, EX2051) (inventors "discovered unexpectedly that [they] could deliver more treprostinil in a shorter period of time with fewer side effects (increasing the treprotinil [sic] dose more than 10-fold compared with iloprost…was not obvious to anyone")).

Prostacyclin analogues were known to produce dose limiting adverse side effects. EX2036. For example, intravenous epoprostenol and intravenous treprostinil can induce headache, nausea, chest pain, jaw pain, backache and restlessness at certain concentrations. *Id.* EX2037 teaches that the maximum tolerated dose for intravenous treprostinil is 24.6 ± 4.0 ng/kg/min. Based on Dr. Hill's assumptions for a person's weight between 60 and 65 kg, the average maximal tolerated dose would have been between 1.47 micrograms/min and 1.59 micrograms/min. Even if a person were to take an entire minute to inhale the one to three breaths, the dosage of 15 micrograms to 90 micrograms, would be an order of magnitude larger than what was considered the maximal tolerated dose. *See also* EX2055, 113:23-114:10 (testifying that if he applied the calculation described in paragraph 100 of his report to the maximal tolerated dose of intravenous treprostinil the maximal tolerated dose of inhaled treprostinil should be 53.125 micrograms).

As of the priority date, only one approved inhalation therapy for the treatment of pulmonary hypertension – Ventavis® (iloprost) – was available. EX1029. Ventavis® was approved for a single event dose of 2.5 micrograms or 5 micrograms

to be taken 6 to 9 times per day. Even at these doses, at least 39% of patients experienced at least one adverse event. *Id.* at 8. The Ventavis® label further teaches – in a study where health volunteers were given inhaled doses of iloprost solution every 2 hours increasing from 5 mcg to up to 20 mcg – 32% of subjects failed to reach the highest scheduled dose. Both iloprost and treprostinil are prostacyclin analogs. A POSA reading the iloprost label, would not have thought that dosages as high as 15 micrograms to 90 micrograms delivered in 1 to 3 breaths would have been well tolerated.

B. Copying

Petitioner's deliberate copying of Tyvaso®, Patent Owner's commercial product embodying the claimed invention, is further evidence of nonobviousness of the claimed inventions. *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1136 (Fed. Cir. 2019) (copying by a competitor is evidence of nonobviousness) (citing *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)). Petitioner's commercial product is referred to in its press releases, corporate filings, patents and publications as LIQ861. LIQ861 is an inhaled, dry-powder formulation of treprostinil. It comes in four "capsule strengths" ranging from approximately 25 to 100 micrograms. EX2084. In clinical trials, LIQ861 has been administered using the Plastiape RS00 Model 8 dry powder inhaler in 2 breaths per capsule. *Id.* at 2. The pharmacokinetics and bioavailability of a 79.5 microgram capsule dose (which

delivers a single event dose of approximately 58.1 micrograms) was directly compared with Patent Owner's commercial product. EX2085. This study demonstrated that Petitioner's commercial product had comparable treprostinil bioavailability with Tyvaso® when delivered in a similar dosage range. *Id.* at Abstract, 5; *see also* EX2036.

Evidence of copying is further supported by Petitioner's patent filings, which disclose that LIQ861 can deliver a single event dosage of treprostinil between 15 micrograms to 90 micrograms in 1 to 3 breaths. EX2088. Finally, Petitioner has chosen to submit an NDA to the FDA for LIQ861 under the 505(b)(2) regulatory pathway with Tyvaso® as the reference listed drug – relying in part on FDA's previous findings of efficacy and safety of Tyvaso® for the treatment of PAH. EX2089, 3.

Comparison of Claims of '793 Patent to LIQ861

Claim 1	LIQ861
1. A method of treating pulmonary hypertension comprising	"***LIQ861 is*** an investigational, inhaled, dry-powder formulation of treprostinil…***for the treatment of PAH***" EX2084, 2 "Based on these results, a phase 3 study (INSPIRE; Clinicaltrials.gov Identifier NCT03399604) evaluating the long-term safety and tolerability of ***LIQ861 in patients with pulmonary arterial hypertension*** was initiated." EX2084, Abstract

administering by inhalation to a human suffering from pulmonary hypertension	"***LIQ861*** is an investigational, ***inhaled***, dry-powder formulation of treprostinil…" EX2084, 2
a therapeutically effective single event dose of a formulation	"***LIQ861*** has the potential to overcome the limitations of current inhaled therapies and to maximize the therapeutic benefits of treprostinil for the treatment of PAH by safely delivering high doses into the lungs in ***one to two breaths***." EX2084, 2 "***LIQ861***…safely delivering doses to the lungs ***in 1 to 2 breaths***." EX2085, Abstract
comprising treprostinil or a pharmaceutically acceptable salt thereof	"***LIQ861 is*** an investigational, inhaled, dry-***powder formulation of treprostinil***…" EX2084, 2
with an inhalation device,	"LIQ861 is an investigational, inhaled, dry-powder formulation of treprostinil designed using Liquidia's PRINTVR technology (Particle Replication in Nonwetting Templates), aiming to enhance deep-lung ***delivery using a convenient, palm-sized dry-powder inhaler (DPI)***, the Plastiape RS00 Model 8 Device, for the treatment of PAH." EX2084, 2
wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of	"…treprostinil exposure from LIQ861 (79.5 µg capsule [approximate delivered dose of 58.1 µg treprostinil])…" EX2085, Abstract

treprostinil or a pharmaceutically acceptable salt thereof	
delivered in 1 to 3 breaths.	"***LIQ861*** has the potential to overcome the limitations of current inhaled therapies and to maximize the therapeutic benefits of treprostinil for the treatment of PAH by safely delivering high doses into the lungs in ***one to two breaths***." EX2084, 2 "***LIQ861***…safely delivering doses to the lungs ***in 1 to 2 breaths***." EX2085, Abstract
Claim 4	**LIQ861**
4. The method of claim 1,	*See* above
wherein the inhalation device is a dry powder inhaler.	"LIQ861 is an investigational, inhaled, dry-powder formulation of treprostinil designed using Liquidia's PRINTVR technology (Particle Replication in Nonwetting Templates), aiming to enhance deep-lung ***delivery using a convenient, palm-sized dry-powder inhaler (DPI)***, the Plastiape RS00 Model 8 Device, for the treatment of PAH." EX2084, 2
Claim 6	**LIQ861**
6. The method of claim 4,	*See* above
wherein the formulation is a powder.	"***LIQ861*** is an investigational, inhaled, ***dry-powder formulation*** of treprostinil…" EX2084, 2
Claim 7	**LIQ861**
7. The method of claim 6,	*See* above

wherein the powder comprises particles less than 5 micrometers in diameter.	"LIQ861 particles are a precise, uniform size (1µm) and trefoil pollen-like shape." Roscigno, Poster presentation at the Pulmonary Vascular Research Institute (PVRI) 12th Annual World Congress, Jan. 2018. Available online here.

C. Long-Felt Unmet Need

The claimed invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension. *See, e.g., Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) ("Secondary considerations of non-obviousness include . . . [the claimed invention's] satisfaction of a long-felt need."). *First*, inhaled treprostinil is indicated for a broader range of pulmonary hypertension patients than the therapeutics available at the time. *Second,* even for the treatment of pulmonary arterial hypertension, many patients found the existing therapies either intolerable or ineffective.

Inhaled treprostinil is currently approved for pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. *Compare* EX2034 (2021 Tyvaso® label) *with* EX1018. The '793 patent further suggests that inhaled treprostinil in doses of 15 to 90 micrograms may also be effective for other types of pulmonary hypertension. *See, e.g.,* EX1001, 9:44-50 (explaining that the study described in example 1 included patients with idiopathic PAH, PAH other,

chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary fibrosis).

As of May 2006 – in fact, even as of January 28, 2021 – no therapies were approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. EX2060, 325. As Petitioner's own expert acknowledged, there is "a completely unmet medical need" where "[t]here [is] nothing that these patients were getting as a therapy for their problems." EX2056, 105:6-8 (discussing the unmet need provided by Pulmozyme).

Even where other therapies had been approved, for example, for the treatment of pulmonary arterial hypertension, there still existed a need for the inhaled dosing regimen described in the claims of the '793 patent. By Petitioner's own admission, the claimed invention of the '793 patent satisfies a long-felt unmet need. EX2089, F-7. In promoting its own product, LIQ861 – which infringes and is an embodiment of the claimed invention, Petitioner touts that the claimed invention as embodied by LIQ861 satisfies a long-felt unmet need. EX2085. ("Given the comparable treprostinil bioavailability and similar safety profiles of LIQ861 and Tyvaso®, LIQ861 fulfills a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler").

VI. CONCLUSION

For the foregoing reasons, the claims are patentable over the cited grounds, and Petitioner has not carried its burden to prove unpatentability.

Respectfully submitted,

By /Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264

Date November 10, 2021

FOLEY & LARDNER LLP
3000 K St., NW
Washington Harbour
Washington, DC 20007
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this Patent Owner Response complies with the type-volume limits of 37 C.F.R. § 42.24(b)(1) because it contains 13,906 words (which is less than the 14,000 permitted), according to the word-processing system used to prepare this Patent Owner Preliminary Response, excluding the portions exempted by 37 C.F.R. 42.24(a)(1)).

Date November 10, 2021

By <u>/Stephen B. Maebius/</u>
Stephen B. Maebius
Registration No. 35,264

FOLEY & LARDNER LLP
3000 K St., NW
Washington Harbour
Washington, DC 20007
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner Response and accompanying Exhibits was served on counsel of record for Petitioner on November 10, 2021 by delivering a copy via email to the counsel of record for the Petitioner at the following addresses:

zLiquidiaIPR@cooley.com
ielrifi@cooley.com
emilch@cooley.com
dkannappan@cooley.com
ssukduang@cooley.com

Date November 10, 2021
FOLEY & LARDNER LLP
3000 K St., NW
Washington Harbour
Washington, DC 20007
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

By /Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264

EXHIBIT 15

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYVASO safely and effectively. See full prescribing information for TYVASO.

TYVASO® (treprostinil) inhalation solution, for oral inhalation use
Initial U.S. Approval: 2002

---------------------------RECENT MAJOR CHANGES---------------------------

Warnings and Precautions (5.4) 05/2022

--------------------------- INDICATIONS AND USAGE---------------------------

Tyvaso is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

----------------------DOSAGE AND ADMINISTRATION----------------------

- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths per treatment session at approximately 1- to 2-week intervals, if tolerated. (2.1)
- Titrate to target maintenance doses of 9 to 12 breaths per treatment session, 4 times daily. (2.1)

--------------------- DOSAGE FORMS AND STRENGTHS---------------------

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

------------------------------ CONTRAINDICATIONS ------------------------------

None. (4)

----------------------- WARNINGS AND PRECAUTIONS -----------------------

- Tyvaso may cause symptomatic hypotension. (5.1)
- Tyvaso inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.3)
- May cause bronchospasm: Patients with a history of hyperreactive airway disease may be more sensitive. (5.4)

------------------------------ ADVERSE REACTIONS ------------------------------

Most common adverse reactions (≥4%) are cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea, and syncope. (6)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

1.2 Pulmonary Hypertension Associated with ILD

Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. Each treatment session will take 2 to 3 minutes. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:
Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil) per treatment session 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:
Dosage should be increased by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals. Studies establishing effectiveness in patients with PAH and PH-ILD have used target doses of 9 to 12 breaths per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.

2.2 Administration

Tyvaso must be used only with the Tyvaso Inhalation System. Patients should follow the instructions for use for operation of the Tyvaso Inhalation System and for daily cleaning of the device components after the last treatment session of the day. To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Tyvaso Inhalation System device.

Do not mix Tyvaso with other medications in the Tyvaso Inhalation System. Compatibility of Tyvaso with other medications has not been studied.

The Tyvaso Inhalation System should be prepared for use each day according to the instructions for use. One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Avoid skin or eye contact with Tyvaso solution. Do not orally ingest the Tyvaso solution.

3 DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso may produce symptomatic hypotension.

5.2 Risk of Bleeding

Tyvaso inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

5.4 Bronchospasm

Like other inhaled prostaglandins, Tyvaso may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk

for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso Inhalation Solution.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):
- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

<u>Pulmonary Arterial Hypertension</u>

In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included cough and throat irritation, headache, gastrointestinal effects, muscle, jaw or bone pain, dizziness, flushing, and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving Tyvaso and More Frequent[a] than Placebo in TRIUMPH I

Adverse Event	Treatment n (%)	
	Tyvaso n=115	Placebo n=120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

[a] More than 3% greater than placebo

The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years, with a maximum exposure of 5.4 years. Eighty-nine percent (89%) of patients achieved the target dose of 9 breaths, 4 times daily. Forty-two percent (42%) achieved a dose of 12 breaths, 4 times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo-controlled trial.

In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough (16.2 vs. 10.9 per 100 patient-years), throat irritation (4.5 vs.

1.2 per 100 pt-years), nasal discomfort (2.6 vs. 1.3 per 100 pt-years), and hemoptysis (2.5 vs. 1.3 per 100 pt-years) compared to the control group.

Pulmonary Hypertension Associated with ILD

In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse reactions were similar to the experience in studies of PAH.

6.2 Post-Marketing Experience

The adverse reaction of angioedema has been identified during the post-approval use of Tyvaso. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.2 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.3 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.3)]*.

7.4 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the international normalized ratio (INR) in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension *(see Clinical Considerations)*. In animal studies, no adverse reproductive and developmental effects were seen for treprostinil at ≥9 and ≥145 times the human exposure when based on C_{max} and AUC, respectively, following a single treprostinil dose of 54 mcg.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-associated maternal and embryo-fetal risk
Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data
Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In studies with orally administered treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC, respectively, following a single Tyvaso dose of 54 mcg. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC, respectively, following a single Tyvaso dose of 54 mcg. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Tyvaso did not include patients younger than 18 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Across clinical studies used to establish the effectiveness of Tyvaso in patients with PAH and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly

patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

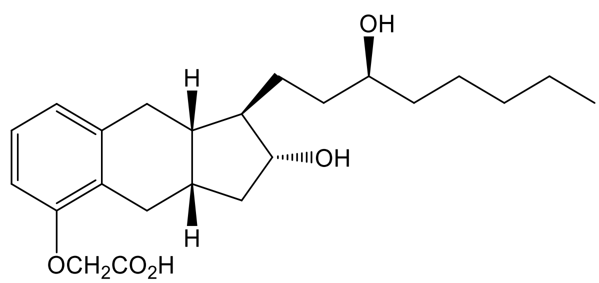
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil, a prostacyclin mimetic, intended for administration by oral inhalation using the Tyvaso Inhalation System. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules, containing 1.74 mg treprostinil (0.6 mg/mL). Each ampule also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate dihydrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is (1*R*,2*R*,3a*S*,9a*S*)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Pharmacokinetic information for single doses of inhaled treprostinil was obtained in healthy volunteers in 3 separate studies. Treprostinil systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the doses administered (18 mcg to 90 mcg).

Absorption

In a 3-period crossover study, the bioavailability of 2 single doses of Tyvaso (18 mcg and 36 mcg) was compared with that of intravenous treprostinil in 18 healthy volunteers. Mean estimates of the absolute systemic bioavailability of treprostinil after inhalation were approximately 64% (18 mcg) and 72% (36 mcg).

Treprostinil plasma exposure data were obtained from 2 studies at the target maintenance dose, 54 mcg. The mean C_{max} at the target dose was 0.91 and 1.32 ng/mL with corresponding mean T_{max} of 0.25 and 0.12 hr, respectively. The mean AUC for the 54-mcg dose was 0.81 and 0.97 hr•ng/mL, respectively.

Distribution

Following parenteral infusion, the apparent steady state volume of distribution (V_{ss}) of treprostinil is approximately 14 L/70 kg ideal body weight.

In vitro treprostinil is 91% bound to human plasma proteins over the 330 to 10,000 mcg/L concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10 to 15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and 1 is a glucuroconjugated derivative (treprostinil glucuronide).

The elimination of treprostinil (following subcutaneous administration of treprostinil) is biphasic, with a terminal elimination half-life of approximately 4 hours using a 2-compartment model.

Specific Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Use in Specific Populations (8.6)]*.

Renal Impairment

In patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre- and post-dialysis resulted in $AUC_{0\text{-}inf}$ that was not significantly altered compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year rat carcinogenicity study was performed with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10, and 20 mg/kg/day in males and 0, 3, 7.5, and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

13.2 Animal Toxicology and/or Pharmacology

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid- and high-dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high-dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed higher incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid- and high-dose levels were about 15 and 35 times, respectively, the clinical exposure at the target maintenance dose of 54 mcg.

14 CLINICAL STUDIES

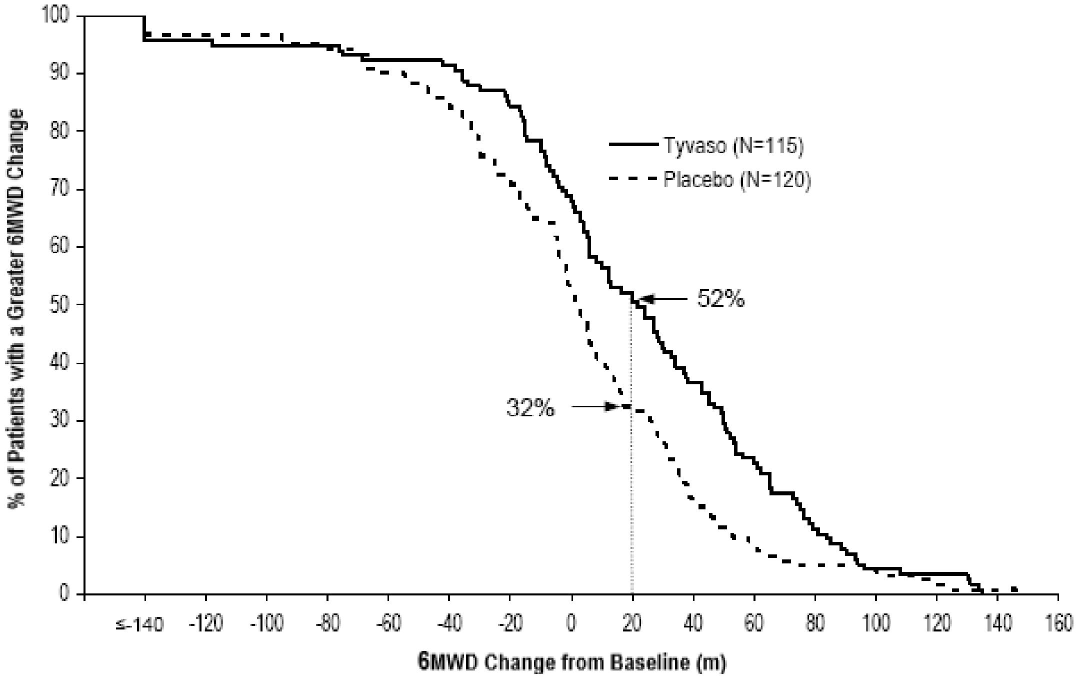
14.1 Pulmonary Arterial Hypertension (WHO Group 1)

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients with PAH. The study population included 235 clinically stable subjects with PAH (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least 3 months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominately female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in 6-Minute Walk Distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3 to 5 hours after bosentan or 0.5 to 2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at

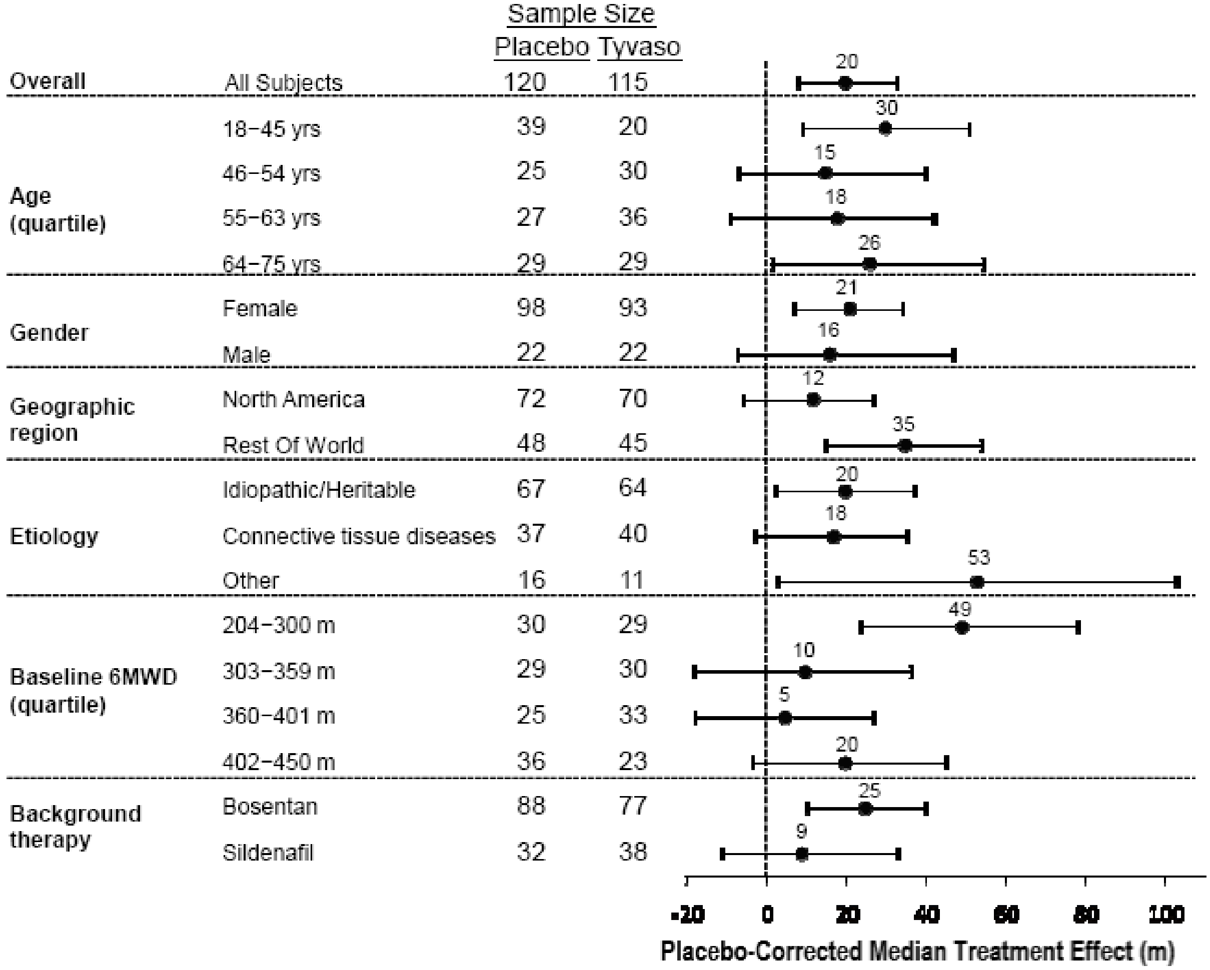
least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso



The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

Figure 2: Placebo-Corrected Median Treatment Effect (Hodges-Lehmann Estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups



14.2 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (N=206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. These uncontrolled observations do not allow comparison with a control group not given Tyvaso and cannot be used to determine the long-term effect of Tyvaso on mortality.

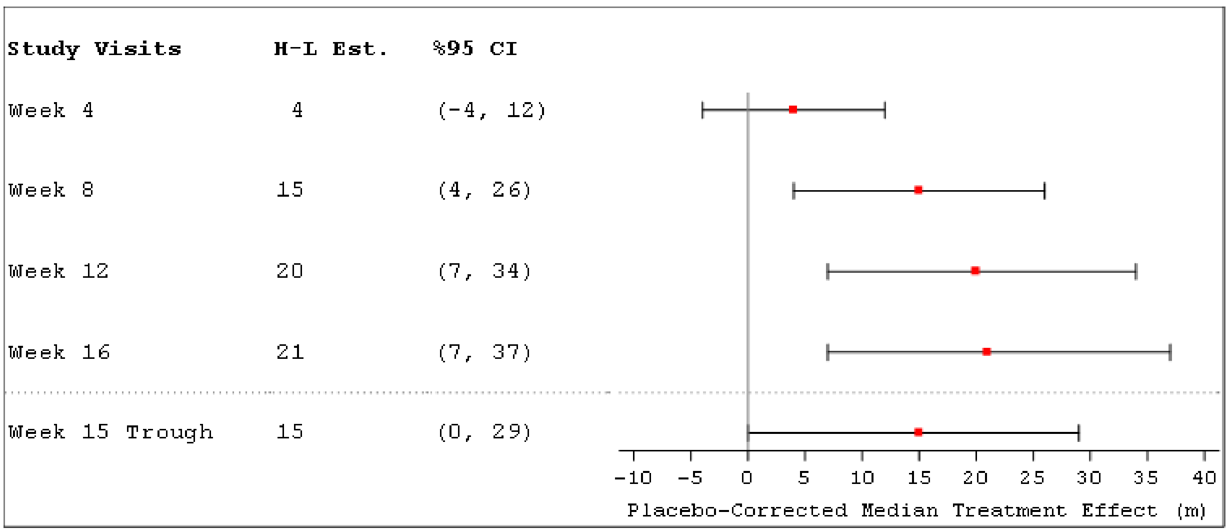
14.3 Pulmonary Hypertension Associated with ILD (WHO Group 3)

INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

Patients in the INCREASE study were randomized (1:1) to either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of patients randomized to Tyvaso titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to Tyvaso reaching a dose of 12 breaths, 4 times daily during the study.

The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 (p=0.004) using Hodges-Lehmann estimate (Figure 3).

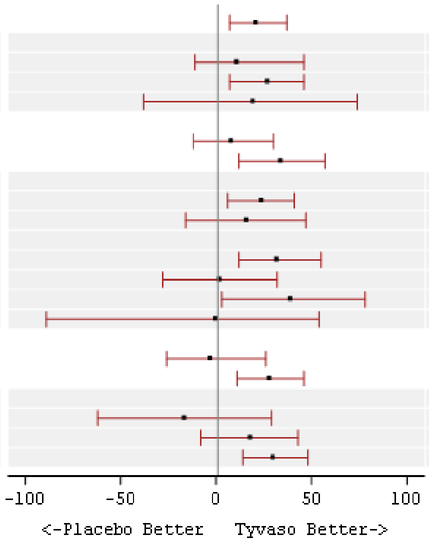
Figure 3: Hodges-Lehmann Estimate of Treatment Effect by Visit for 6MWD at Peak Exposure (PH-ILD)



The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose (Figure 4).

Figure 4: Forest Plot on Subgroup Analyses of Peak 6MWD (Meter) at Week 16 (PH-ILD)

Subgroup	Tyvaso (# of Patients)	Placebo (# of Patients)	H-L Estimate (95% CI)	p-value
Overall	163	163	21.0(7.0, 37.0)	0.0043
Age Group				
<65 years old	64	48	11.0(-11.0, 46.0)	0.3203
65 - <80 years old	83	100	27.0(7.0, 46.0)	0.0111
>=80 years old	16	15	19.5(-38.0, 74.0)	0.9457
Sex				
Male	78	95	8.0(-12.0, 30.0)	0.4877
Female	85	68	34.0(12.0, 57.0)	0.0010
Baseline 6MWD Category				
<=350 meters	136	133	24.0(6.0, 41.0)	0.0084
>350 meters	27	30	16.0(-16.0, 47.0)	0.2697
PH-ILD Etiology				
IIP	65	81	32.0(12.0, 55.0)	0.0030
CPFE	42	40	2.0(-28.0, 32.0)	0.8742
CTD	40	32	39.0(3.0, 78.0)	0.0317
Other	16	10	0.0(-89.0, 54.0)	0.3607
Baseline PVR Category				
<4 WU	32	34	-3.0(-26.0, 26.0)	0.7345
>=4 WU	131	129	28.0(11.0, 46.0)	0.0019
Maximum Study Drug Dose				
4-6 breaths	6	2	-16.5(-62.0, 29.0)	0.8481
7-9 breaths	37	24	18.0(-8.0, 43.0)	0.2875
>=10 breaths	78	94	30.0(14.0, 48.0)	0.0006



Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD >15% from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with Tyvaso in patients with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups (Table 2). Overall, treatment with Tyvaso demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test p=0.041; Figure 5), and a 39% overall reduction in the risk of a clinical worsening event (HR=0.61 [95% CI; 0.40, 0.92]; Figure 5).

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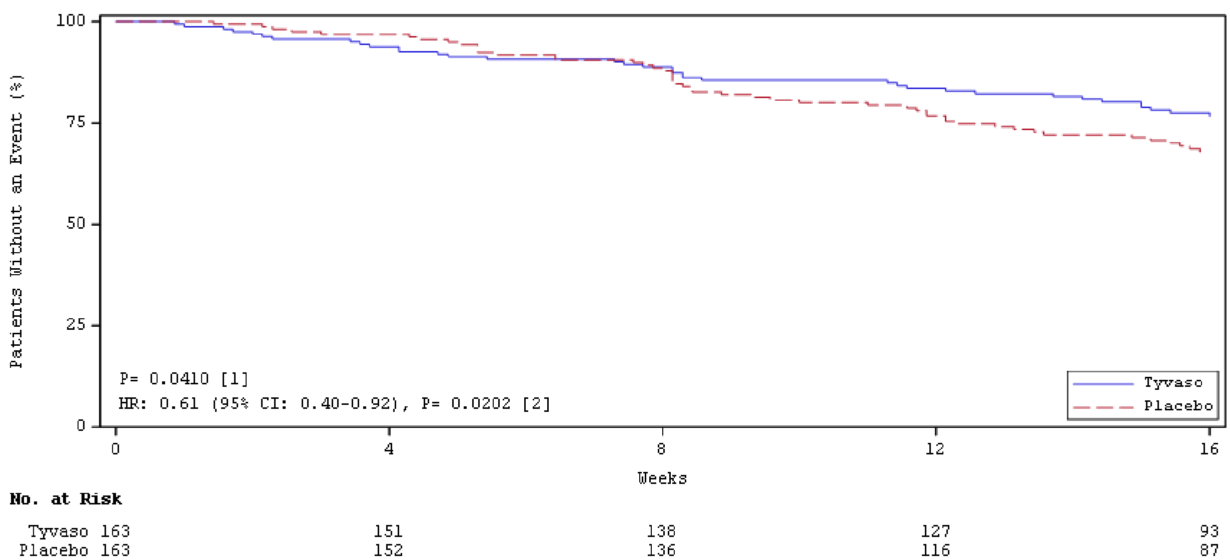
Table 2: Clinical Worsening Events (PH-ILD)

		Tyvaso n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
Clinical worsening		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
First contributing event	**Hospitalization due to a cardiopulmonary indication**	18 (11.0%)	24 (14.7%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	13 (8.0%)	26 (16.0%)	
	Death (all causes)	4 (2.5%)	4 (2.5%)	
	Lung transplantation	2 (1.2%)	0	
First of each event	**Hospitalization due to a cardiopulmonary indication**	21 (12.9%)	30 (18.4%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	16 (9.8%)	31 (19.0%)	
	Death (all causes)	8 (4.9%)	10 (6.1%)	
	Lung transplantation	2 (1.2%)	1 (0.6%)	

Figure 5: Kaplan-Meier Plot of Time to Clinical Worsening Events (PH-ILD)



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16 HOW SUPPLIED/STORAGE AND HANDLING

Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as 4 ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL.

Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days. Because Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch.

One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than 1 day (24 hours). Any remaining solution should be discarded at the end of the day.

Tyvaso Inhalation System Starter Kit containing a 28-ampule carton of Tyvaso (7 foil pouches each containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and the Tyvaso Inhalation System. (NDC 66302-206-01)

Tyvaso Inhalation System Refill Kit containing a 28-ampule carton of Tyvaso (7 foil pouches each containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and accessories. (NDC 66302-206-02)

Tyvaso 4 Pack Carton with 1 foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL). (NDC 66302-206-03)

Tyvaso Inhalation System Institutional Starter Kit containing a 4-ampule carton of Tyvaso (1 foil pouch containing four 2.9 mL ampules; each ampule contains 1.74 mg treprostinil [0.6 mg per mL]) and the Tyvaso Inhalation System. (NDC 66302-206-04)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Train patients in the administration process for Tyvaso, including dosing, Tyvaso Inhalation System set up, operation, cleaning, and maintenance, according to the instructions for use *[see Dosage and Administration (2.1, 2.2)]*.

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Tyvaso Inhalation System device *[see Dosage and Administration (2.2)]*.

In the event that a scheduled treatment session is missed or interrupted, resume therapy as soon as possible *[see Dosage and Administration (2.1)]*.

If Tyvaso comes in contact with the skin or eyes, instruct patients to rinse immediately with water *[see Dosage and Administration (2.2)]*.

Tyvaso manufactured for:

United Therapeutics Corp.
Research Triangle Park, NC 27709

EXHIBIT 16

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 20-755 (RGA) (JLH) **HIGHLY CONFIDENTIAL**

INITIAL EXPERT REPORT OF ANDREW CLARK, PH.D.

Table of Contents

I. INTRODUCTION

A. Scope of Analysis

1. I have been retained by counsel for the Plaintiff, United Therapeutics Corporation ("UTC") to provide expert opinions related to U.S. Patent No. 10,716,793 (the "'793 patent").

2. I have been informed that Liquidia has filed a New Drug Application No. 213005 with the FDA ("Liquidia NDA") seeking approval to manufacture, market, and sell a generic copy of UTC's TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/ml that is approved by FDA for treatment of pulmonary arterial hypertension ("Liquidia's Proposed Product").

3. I have been informed that UTC has asserted that Liquidia's Proposed Product infringes claims 1, 4, and 6-8 of the '793 patent (the "Asserted Claims") when used in the intended manner and as taught and described in Liquidia's proposed label/package insert ("Liquidia's Proposed Label")[1], Liquidia's Proposed Instructions for Use[2], and other NDA documentation.

4. I have been asked to opine on whether, upon FDA approval, administration of Liquidia's Proposed Product, as described in Liquidia's Proposed Label, Instructions for Use, and related NDA documentation, would infringe the asserted claims of the '793 patent. I have also been asked to give my opinion as to whether Liquidia induces or contributes to infringement.

5. This report presents my opinions regarding infringement of the '793 patent and lays out the bases for my opinions. My opinions are based on my education, research, professional experience, and the materials that I reviewed in preparing the opinions described in this report.

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[1] Liquidia's Proposed Label (LIQ02790995-LIQ02791011) at LIQ02790995.
[2] Liquidia's Proposed Instructions for Use (LIQ00029269) at LIQ00029269.

6. My opinions and the bases for them are based on presently available information that I have reviewed and that I am currently aware exists. I understand that discovery is ongoing in this case, and more information or documents may therefore become available. For example, I understand that there are a number of outstanding depositions, including of a Liquidia corporate representative, LGM Pharma, LLC, Dr. Lewis Rubin, and others. I further understand that there continues to be additional non-testimonial discovery, including amendments to interrogatory responses and discovery of documents from the parties and/or from third parties. Accordingly, I reserve the right to take into account further information that I may learn, and adjust, modify, or supplement my opinions based on any additional information that I become aware of.

7. If asked to testify at trial, I may rely on physical objects, samples, visual aids, and demonstrative exhibits, such as claim charts and graphs, to demonstrate the bases for my opinions.

8. I am being compensated for my time spent on this matter at the rate of $400 per hour plus reimbursement of reasonable expenses. I have no other interest in this litigation or in any party to this litigation. My compensation does not depend on my performance, the substance of my opinions, the outcome of the case, or any issues involved in or related to this case.

B. Qualifications

9. My *curriculum vitae*, which is attached as **Exhibit 1**, summarizes my professional experience. I provide below further details about my experience that may be pertinent to this matter.

10. I am currently President and General Manager of the Aerogen Pharma Corporation. Aerogen Pharma is dedicated to the development of drug device combination products for

59. In view of the foregoing evidence, and presumably from his perspective as a clinician, I understand that Dr. Waxman has interpreted a "single event dose" to refer to a single treatment session. I agree with that interpretation, rely on it, and note that it is consistent with the '793 patent specification and claims. [redacted]

60. Regarding therapeutic effectiveness, as an initial matter, in my experience, companies generally do not seek approval for drugs that lack any benefit to the patient; indeed, my understanding is that FDA approval requires showing safety and efficacy.[51] [redacted]

61. Further, the '793 provides explanation and hemodynamic data showing a beneficial effect on the patient.[52] In addition to the descriptions in the text, the Figures show a beneficial effect. For example, Figure 1 shows a reduction in pulmonary arterial pressure ("PAP") and pulmonary vascular resistance ("PVR") relative to placebo upon administration of 30, 45, and 60 µg of treprostinil.[53] In view of the foregoing evidence, I understand that Dr.

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[50] Liquidia's Proposed Label at LIQ02790996.
[51] *See, e.g.*, FDA, The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, *available at* https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.
[52] *See, e.g.*, U.S. Patent No. 10,716,793 at 9:5-34 (describing administration of 30 µg, 45 µg, and 60 µg of treprostinil that achieved reduction of PVR for longer than two hours); *id.* at 8:67-9:3 (delivery of 30, 60, 90 µg of treprostinil through ultrasonic nebulizer reduced PVR for up to 3 hours); *see also id.* at Tables I-III.
[53] *See also id*. Figs. 2-11.

Waxman has concluded that single doses of treprostinil have a beneficial effect on patients. I agree with that conclusion, rely on it, and, in my opinion, it is supported by the data (including the hemodynamic data) in the '793 patent.

62. [redacted] As such, it is my opinion that patients following Liquidia's Proposed Label and Instructions for Use will administer a therapeutically effective single event dose.

d) "of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof"

63. It is my opinion that administration of Liquidia's Proposed Product as described in Liquidia's Proposed Label and Liquidia's Proposed Instructions for Use and other documentation results in administration of "a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof."

64. [redacted]

65. These documents make clear that LIQ861 is a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof.

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[54] Liquidia's Proposed Label at LIQ02790995.
[55] *Id*. at LIQ02791003; see also Deposition of Tushar Shah, Sept. 24, 2021, at p. 42:22-24.
[56] Liquidia's Proposed Instructions for Use at LIQ00029269.
[57] Pre-IND Briefing at LIQ00000696.

EXHIBIT 17

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	C.A. No. 20-755 (RGA) (JLH) **HIGHLY CONFIDENTIAL**

<u>INITIAL EXPERT REPORT OF AARON WAXMAN, M.D., Ph.D.</u>

Table of Contents

I. Introduction

A. Purpose of Report

1. I have been retained by counsel for the Plaintiff, United Therapeutics Corporation ("UTC") as an expert consultant. I may provide expert testimony related to U.S. Patent No. 10,716,793 ("the '793 patent") and regarding the background and understanding of pulmonary hypertension ("PH") and/or pulmonary arterial hypertension ("PAH") and the treatment of the same with inhaled treprostinil. I understand that Liquidia is seeking approval for LIQ861, an inhaled dry powder formulation of treprostinil, and has filed an NDA with the FDA (the "LIQ861 NDA").[1] I may provide expert testimony regarding whether the product described in the LIQ861 NDA ("Liquidia's Proposed Generic Product"), including as taught in Liquidia's proposed label/package insert ("Liquidia's Proposed Label")[2] and as taught in Liquidia's Proposed Instructions for Use,[3] infringes the claims of the '793 patent. This report presents my opinions regarding the alleged infringement of the '793 patent and the bases for the opinions.

2. I am being compensated for the time I spend at the rate of $500 per hour. My compensation does not depend on the outcome of the case, and I am not

[1] Throughout this report, I may refer to the proposed product described in Liquidia's NDA and relevant documentation, such as the label and instructions for use, as "Liquidia's Proposed Product" or "LIQ861."
[2] *E.g.*, LIQ02790995.
[3] *E.g.*, LIQ00029269.

affiliated with or employed by Plaintiff UTC or Defendant Liquidia Technologies, Inc.

B. Materials Considered

3. To form my opinions I have reviewed and/or relied on the documents and things listed in **Exhibit 1**, attached, or referenced in the text or footnotes of this report as well as my educational and professional experience. My opinions and the bases for them are based on information that I know and that I have reviewed. I may use the materials I have cited or listed, including those attached hereto, in order to assist me in preparing demonstratives such as graphics, models, and animations for my testimony.

4. I reserve the right to adjust, modify or supplement my opinions in light of any response, critique, or comments on my report or different opinions made by or on behalf of Liquidia, including, but not limited to, any deposition testimony or rebuttal reports that Liquidia's experts submit.

5. I understand that discovery is ongoing in this case, and more information or documents may therefore become available. For example, I understand that there are a number of outstanding depositions, including of a Liquidia corporate representative, LGM Pharma, LLC, Dr. Lewis Rubin, and others. I further understand that there continues to be additional non-testimonial discovery, including amendments to interrogatory responses and discovery of documents from

[redacted]

[redacted] [redacted] It is my opinion that the INSPIRE study indicates that that the prescribed doses of delivered treprostinil Liquidia has proposed are "therapeutically effective."

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70 *Id*.

71 Liquidia's Proposed Label at LIQ02791006–02791009 at LIQ02791007.

74. Another clinical study—referred to as "TRIUMPH I"—was a 12-week, randomized, double blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable patients with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan or sildenafil for at least three months prior to the study initiation. These patients were administered either placebo or treprostinil inhalation solution (*e.g.*, Tyvaso) in four daily treatment sessions (i.e. single event doses) with a target single event dose of 9 breaths (54 micrograms) per session over the course of the 12 week study. The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. Patients receiving single event dosages of 54 micrograms had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12. In my opinion, these results indicate that a single event dosage of 54 micrograms is therapeutically effective.

75. With my significant experience in the field, it is also clear that the only reason to put a patient suffering from pulmonary hypertension on a drug like LIQ861 would be to introduce to the patient a therapeutically effective amount of the drug. There would be nothing to gain from giving a patient an amount of the drug that would not be effective to do what it needs to do. By intending to provide and sell LIQ861, Liquidia demonstrates its intent for physicians to prescribe and patients to

administer LIQ861 in an amount that would help the patient. Similarly, for patients and caretakers, the reason to take the drug is for the benefit, so patients and caretakers would be induced by the product to receive a therapeutically effective amount.

76. [redacted]

77. My opinion regarding "therapeutically effective" is further supported by the fact that [redacted]

[72] LIQ861 NDA Resubmission 3.2.P.5.6 Response to Complete Response Justification of Specifications (LIQ02793078–02793104) at LIQ02793085.
[73] LIQ861 NDA 3.2.5.1 Specification(s) (LIQ00030834–00030847) at LIQ00030835–00030847.

EXHIBIT 18

Deposition of:

Andrew Clark, Ph.D.

January 14, 2022

In the Matter of:

United Therapeutics Corporation vs Liquidia Technologies Inc

Veritext Legal Solutions
800-734-5292 | calendar-dmv@veritext.com |

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

____

	)Case No.
UNITED THERAPEUTICS	)1:20-cv-00755
CORPORATION	)
	)
Plaintiff	)
	)
vs.	)
	)
LIQUIDIA TECHNOLOGIES, INC.,	)
	)
Defendant	)

____

\- HIGHLY CONFIDENTIAL -

Remote Videotaped Deposition of

ANDREW CLARK, Ph.D.

January 14, 2022

9:00 a.m.

Reported by: Bonnie L. Russo
Job No. 5008733

Remote Videotaped Deposition of Andrew Clark, Ph.D. held through:

Veritext Legal Solutions
1250 I Street, N.W.
Washington, D.C.

Pursuant to Notice, when were present on behalf of the respective parties:

APPEARANCES:
On behalf of the Plaintiff:
ART DYKHUIS, ESQUIRE
McDERMOTT WILL & EMERY
2049 Century Park E
Suite 3200
Los Angeles, California 90067
adykhuis@mwe.com
-and-
TIMOTHY DUNKER, ESQUIRE
McDERMOTT WILL & EMERY
500 N. Capitol Street, N.W.
Washington, D.C. 20001
tdunker@mwe.com
On behalf of the Defendant:
LAUREN KRICKL, ESQUIRE
COOLEY LLP
3175 Hanover Street
Palo Alto, California 94304
lkrickl@cooley.com
-and-
DOUGLAS WILLIAM CHEEK, ESQUIRE
JONATHAN DAVIES, ESQUIRE
COOLEY LLP
1299 Pennsylvania Avenue, N.W.
Suite 700
Washington, D.C. 20004
dcheek@cooley.com
jdavies@cooley.com
-and-
BRITTANY CAZAKOFF, ESQUIRE
COOLEY LLP
11951 Freedom Drive
1 Freedom Square
Reston Town Center
Reston, Virginia 20190
bcazakoff@cooley.com

Also Present:
Orson Braithwaite, Videographer

I N D E X

EXHIBITS

EXHIBITS (CONTINUED):

EXHIBITS (CONTINUED):

(Exhibits bound separately.)

P R O C E E D I N G S

(9:00 a.m.)

12:00:48

THE VIDEOGRAPHER: Good morning. 12:00:48

We are going on the record at 9:00 12:00:58
a.m. on January 14, 2022. This is Media Unit 1 12:01:00
of the remote-recorded deposition of Dr. Andrew 12:01:05
Clark in the matter of United Therapeutics 12:01:09
Corporation versus Liquidia Technologies, Inc., 12:01:11
filed in the United States District Court for 12:01:14
the District of Delaware, Case No. 20-755. 12:01:18

My name is Orson Braithwaite from 12:01:22
the firm Veritext Legal Solutions, and I am the 12:01:24
videographer. The court reporter is Bonnie 12:01:26
Russo from the firm Veritext Legal Solutions. 12:01:29

Counsel will now state their appears 12:01:31
and affiliations for the record. 12:01:34

MS. KRICKL: Lauren Krickl of Cooley 12:01:36
on behalf of defendant, Liquidia, and with me 12:01:38
is Brittany Cazakoff and Doug Cheek, and John 12:01:41
Davies will be joining later. 12:01:45

MR. DYKHUIS: Art Dykhuis on behalf 12:01:47

of United Therapeutics Corporation. I am with McDermott Will & Emery. Also with me is Tim Dunker from McDermott for UTC. 12:01:51 12:01:54 12:01:58

THE VIDEOGRAPHER: Thank you. 12:02:01

Will the court reporter please swear in the witness. 12:02:02 12:02:03

THE COURT REPORTER: Yes. First, I have a stipulation to put on the record.

The attorneys participating in this deposition acknowledge that I am not physically present in the deposition room and that I will be remote -- reporting this deposition remotely.

They further acknowledge that, in lieu of an oath administered in person, I will administer the oath remotely.

The parties further agree that if the witness is testifying from a state where I am not a notary, that the witness may be sworn in by an out-of-state notary.

If any party has an objection to this manner of reporting, please state it now.

(Pause.)

THE COURT REPORTER: Hearing none, we can proceed and I will swear in the witness.

ANDREW CLARK, Ph.D.

being first duly sworn, to tell the truth, the whole truth, and nothing but the truth, testified as follows:

EXAMINATION BY COUNSEL FOR DEFENDANT 12:02:48

BY MS. KRICKL: 12:02:48

Q. Good morning, Dr. Clark. 12:02:49
A. Good morning. 12:02:50
Q. Please state your full name for the 12:02:51 record. 12:02:54
A. Andrew Reginald Clark. 12:02:54
Q. Do you understand that you just 12:02:56 swore under oath to tell the truth at this 12:02:58 deposition today? 12:03:01
A. I did, yes. 12:03:01
Q. Do you understand that the testimony 12:03:03 you give will be just as binding as if you were 12:03:04 sitting in court today? 12:03:08

A. Yes, I do. 12:03:09

Q. Is there any reason why you cannot completely and truthfully answer my questions today? 12:03:10 12:03:12 12:03:14

A. Nope. 12:03:15

Q. Have you testified before at a deposition? 12:03:16 12:03:19

A. Nope. 12:03:19

Q. I'll just go over a few ground rules. 12:03:21 12:03:21

If you do not understand a question, please let me know. Otherwise, I'll assume that you understood. Okay? 12:03:24 12:03:26 12:03:31

A. Yep. 12:03:31

Q. Do you understand that we can't speak over each other to help the court reporter? 12:03:31 12:03:34 12:03:37

A. Yes. Understood. 12:03:37

Q. And the court reporter can't record a nod or gestures, so you will need to make a verbal response to my question, please. 12:03:38 12:03:41 12:03:45

A. Yes. Understood. 12:03:47

course, spending an awful lot of money running 12:51:35
very large Phase 3 trials. 12:51:38

Q. Can you explain to me how 12:51:45
pharmacological effects relate to hemodynamics? 12:51:47

MR. DYKHUIS: Objection to form. 12:51:50

THE WITNESS: In the case of -- 12:51:52

Sorry, art. Do you want to -- 12:51:53

MR. DYKHUIS: Yeah. I -- I'm done. 12:51:58
Just objected to form. Thank you. 12:52:00

THE WITNESS: Okay. All right. 12:52:01
I -- I -- I got to slow down there a little bit 12:52:02
here. 12:52:04

Can you repeat the question. 12:52:04

BY MS. KRICKL: 12:52:06

Q. Yeah. I'm just trying to 12:52:06
understand. You mentioned pharmacological 12:52:07
effect. Does -- does that relate to 12:52:10
hemodynamics in any way? 12:52:13

A. Yeah. Essentially, what these 12:52:16
molecules do is they cause dilation of the 12:52:20
pulmonary vasculature which reduces the 12:52:24
pulmonary vascular resistance which reduces the 12:52:28

pulmonary artery pressure, and that's a prerequisite to having a long-term clinical benefit. 12:52:31 12:52:34 12:52:36

Q. What do you mean when you say "long-term clinical benefit"? 12:52:39 12:52:43

A. In terms of the patient feeling some effect in terms of exercise capacity or -- yeah. I mean, exercise capacity. Leave it at that. 12:52:45 12:52:54 12:53:00 12:53:04

So the clinical benefit as described in the 79 -- '793 patent is actually its effects on the malady that causes pulmonary arterial hypertension, and it's clinically effective in improving hemodynamics. 12:53:06 12:53:09 12:53:13 12:53:19 12:53:23

Q. And you -- you just -- I apologize if I am misstating, but you said those -- those improvement in hemodynamics are a prerequisite for having long-term clinical benefit? 12:53:30 12:53:36 12:53:42 12:53:46

MR. DYKHUIS: Object to form. 12:53:48

THE WITNESS: Yes. The -- the -- the -- the disease of pulmonary arterial hypertension is relieved by dilating the 12:53:53 12:53:56 12:53:59

pulmonary vasculature and, hence, reducing pulmonary artery pressure. And that's what these drugs do. 12:54:05 12:54:10 12:54:12

BY MS. KRICKL: 12:54:13

Q. So it's your opinion that a drug is therapeutically effective if it benefits the patient in terms of hemodynamic data, right? 12:54:13 12:54:16 12:54:17

A. Correct. Yeah. 12:54:21

Q. And it's also your opinion that a drug is therapeutically effective if it benefits a patient's exercise ability? 12:54:22 12:54:26 12:54:28

MR. DYKHUIS: Objection to form. 12:54:30

THE WITNESS: In the longer term, yes. 12:54:34 12:54:36

BY MS. KRICKL: 12:54:36

Q. So you agree that a drug is therapeutically effective if it in the long-term improves how a patient feels, functions, or survives? 12:54:38 12:54:40 12:54:41 12:54:47

MR. DYKHUIS: Objection to form and foundation and to the extent it calls for a legal conclusion. 12:54:48 12:54:53 12:54:53

THE WITNESS: Yeah. I -- I -- I -- 12:54:57
yeah. I would answer that question slightly 12:54:57
differently in that -- in that I interpreted 12:55:00
therapeutically effective in the context of the 12:55:01
specification in the patent which demonstrates 12:55:04
that exercising the claims in the patent 12:55:09
actually improves hemodynamics in the patient 12:55:12
and, therefore, is therapeutically effective. 12:55:15

I do not believe you have to do 12:55:28
long-term, Phase 3 clinical trials to 12:55:31
demonstrate a therapeutic effect. 12:55:35

BY MS. KRICKL: 12:55:37

Q. Understood. But would a drug that 12:55:37
improved how a patient feels, functions, and 12:55:40
survives be considered therapeutically 12:55:43
effective as well? 12:55:45

MR. DYKHUIS: Objection to form. 12:55:47

THE WITNESS: Yeah. It's just a 12:55:50
different definition of therapeutically 12:55:53
effective. 12:55:53

BY MS. KRICKL: 12:55:56

Q. Okay. 12:55:56

A. It doesn't have to do that to be therapeutically effective. 12:56:00 12:56:04

Q. If a pulmonary hypertension drug improved a patient's hemodynamic measures but did not benefit how a patient felt, functioned, or survived, would you consider that drug therapeutically effective? 12:56:05 12:56:08 12:56:11 12:56:15 12:56:17

MR. DYKHUIS: Objection. Form and hypothetical. 12:56:18 12:56:20

You can answer. 12:56:25

THE WITNESS: I mean, it -- it is hypothetical. I have -- I have -- you know, I've got no idea. I would certainly consider it therapeutically effective during development because it affects the correct physiology and has the correct pharmacology. 12:56:26 12:56:26 12:56:30 12:56:35 12:56:37 12:56:41

BY MS. KRICKL: 12:56:43

Q. Are you aware of any pulmonary hypertension drugs that affect a patient's hemodynamics but do not affect how a patient feels, functions, or survives? 12:56:43 12:56:45 12:56:52 12:56:55

MR. DYKHUIS: Object to form. 12:56:57

THE WITNESS: None that I can think of at the moment. 12:57:03 12:57:04

BY MS. KRICKL: 12:57:07

Q. Do you know if the FDA would approve such a drug? 12:57:07 12:57:10

MR. DYKHUIS: Object to form. Scope. 12:57:11 12:57:14

THE WITNESS: I -- that -- that -- that, again, is hypothetical. I'm not sure anybody would ask the FDA to approve, and in the context of the '793 patent, there is no limitation that says the FDA have to approve it on clinical benefit, as opposed to therapeutic benefit, which is demonstrated in the patent. 12:57:16 12:57:17 12:57:25 12:57:27 12:57:31 12:57:34 12:57:37

BY MS. KRICKL: 12:57:40

Q. You said the claims are directed to methods of treatments, though, right? 12:57:40 12:57:44

A. Yes. 12:57:45

Q. Okay. In your experience as a drug developer, would you find a drug that improves hemodynamics but does not improve how a patient feels, functions, or survives lucrative to 12:57:46 12:57:55 12:57:57 12:58:00

EXHIBIT 19

ClinicalTrials.gov

Go to the classic website

Record 1 of 1

The U.S. government does not review or approve the safety and science of all studies listed on this website.

Read our full disclaimer (https://clinicaltrials.gov/about-site/disclaimer) for details.

COMPLETED

Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE

ClinicalTrials.gov ID **NCT02630316**

Sponsor United Therapeutics

Information provided by United Therapeutics (Responsible Party)

Last Update Posted 2022-07-27

Record History Tab

Study Record Versions

- This table shows all the versions of this study record arranged in order by submitted date.
  - To view one version of the study record, click the submitted date.
  - To compare two versions, select them using the check boxes and click "Compare" at the bottom of the list.

	Version	Date submitted (YYYY-MM-DD)	Changes
☐	1	2015-12-11	• None (earliest version on record)
☐	2	2016-02-24	• Recruitment Status • Study Status • Contacts/Locations
☐	3	2016-03-14	• Study Status • Contacts/Locations
☐	4	2016-05-05	• Study Status • Contacts/Locations
☐	5	2016-05-23	• Study Status • Contacts/Locations
☐	6	2016-05-31	• Study Status • Contacts/Locations
☐	7	2016-06-06	• Study Status

Compare

Feedback

	Version	Date submitted (YYYY-MM-DD)	Changes
			• Contacts/Locations
☐	8	2016-06-07	• Study Status • Contacts/Locations
☐	9	2016-06-23	• Study Status • Contacts/Locations
☐	10	2016-07-05	• Study Status • Contacts/Locations
☐	11	2016-07-12	• Study Status • Contacts/Locations
☐	12	2016-07-21	• Study Status • Contacts/Locations • Study Identification
☐	13	2016-08-15	• Recruitment Status • Study Status
☐	14	2016-08-26	• Recruitment Status • Study Status • Contacts/Locations
☐	15	2016-09-09	• Study Status • Eligibility • Study Description
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☐	23	2017-02-09	• Study Status • Contacts/Locations

	Version	Date submitted (YYYY-MM-DD)	Changes
☐	24	2017-03-01	• Study Status • Eligibility • Study Description
☐	25	2017-03-09	• Study Status • Contacts/Locations
☐	26	2017-03-17	• Study Status • Contacts/Locations
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	Version	Date submitted (YYYY-MM-DD)	Changes
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☐	75	2019-04-19	• Study Status

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☐	83	2019-10-28	• Study Status • Contacts/Locations
☐	84	2019-12-20	• Study Status • Contacts/Locations
☐	85	2020-01-07	• Recruitment Status • Study Status • Study Design • Contacts/Locations
☐	86	2020-02-26	• Study Status
☐	87	2020-04-30	• Study Status
☐	88	2020-05-29	• Study Status • Outcome Measures • Contacts/Locations • Oversight • Study Description
☐	89	2021-04-29	• Study Status • Eligibility • Baseline Characteristics • Outcome Measures • Adverse Events • Study Description • Arms and Interventions

	Version	Date submitted (YYYY-MM-DD)	Changes
			• Contacts/Locations • Participant Flow • More Information • Document Section **Quality Control Review Has Not Concluded** Returned: 2021-05-21
☐	90	2021-05-25	• Study Status • Study Description • Outcome Measures • Eligibility • Baseline Characteristics • Adverse Events **Quality Control Review Has Not Concluded** Returned: 2021-06-17
☐	91	2021-06-21	• Study Status • Study Description • Outcome Measures
☐	92	2021-10-11	• Study Status • More Information
☐	93	2022-07-21	• Study Status • Document Section

Version 23: 2017-02-09

Study Details

Study Identification

Unique Protocol ID

RIN-PH-201

Brief Title

Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE

Official Title

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects With Pulmonary Hypertension Due to Parenchymal Lung Disease

Secondary IDs

Study Status

Record Verification	2017-02
Overall Status	Recruiting
Study Start	2016-02
Primary Completion	2018-10 [Estimated]
Study Completion	2018-10 [Estimated]
First Submitted	2015-12-11
First Submitted that Met QC Criteria	2015-12-11
First Posted	2015-12-15
Last Update Submitted that Met QC Criteria	2017-02-09
Last Update Posted	2017-02-10 [Actual]

Sponsor/Collaborators

Sponsor	United Therapeutics
Responsible Party	Sponsor
Collaborators	

Oversight

U.S. FDA-regulated Drug

U.S. FDA-regulated Device

Data Monitoring

Yes

Study Description

Brief Summary

This is a multicenter, randomized (1:1 inhaled treprostinil: placebo), double-blinded, placebo-controlled trial to evaluate the safety and efficacy of inhaled treprostinil in subjects with pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE). The study will include about 314 patients at approximately 100 clinical trial centers. The treatment phase of the study will last approximately 16 weeks. Patients who complete all required assessments will also be eligible to enter an open-label, extension study (RIN-PH-202).

Detailed Description

Conditions

Condition

Pulmonary Hypertension
Interstitial Lung Disease
Combined Pulmonary Fibrosis and Emphysema

Keywords

Treprostinil
PH
ILD
CPFE
6 Minute Walk Test

Study Design

Study Type

Interventional

Primary Purpose

Treatment

Study Phase

Phase 2
Phase 3

Interventional Study Model

Parallel Assignment

Interventional Model Description

Number of Arms
2

Masking
Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Masking Description

Allocation
Randomized

Enrollment
314 [Estimated]

Arms and Interventions

Arms	Assigned Interventions
Placebo Comparator: Placebo Matching placebo inhaled using an ultrasonic nebulizer four times daily	Drug: Placebo • Placebo administered four times daily
Active Comparator: Active Inhaled Treprostinil Active Treprostinil for inhalation solution (0.6 mg/mL) delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Inhaled four times daily and titrated up to a maximum of 12 breaths four times daily	Drug: Inhaled Treprostinil • Inhaled treprostinil (6 mcg/breath) administered four times daily • Other Names: ◦ Tyvaso

Outcome Measures

Primary Outcome Measures

1. Change in 6-minute Walk Distance (6MWD) Measured at Peak Exposure from Baseline to Week 16
   The intent of the 6MWD test is to evaluate exercise capacity associated with carrying out activities of daily living. Change in 6MWD from Baseline to Week 16, correlates with the current clinical standard for assessing patient functional status in the treatment of PH and is considered an objective measure of patient functional status. Subjects will be instructed to walk down a corridor at a comfortable speed as far as they can manage for six minutes. Distance <500 meters suggests considerable exercise limitation; Distance 500-800 meters suggests moderate limitation; Distance >800 meters (with no rests) suggests mild or no limitation. Peak exposure 6MWD will occur by conducting 6-minute walk test (6MWT) within 10 to 60 minutes after the most recent dose of study drug dose.
   [Time Frame: Baseline and Week 16]

Secondary Outcome Measures

1. Change in Peak 6-minute Walk Distance (6MWD) from Baseline to Week 12
   The intent of the 6MWD test is to evaluate exercise capacity associated with carrying out activities of daily living. Change in 6MWD from Baseline to Week 12, correlates with the current clinical standard for assessing patient functional status in the treatment of PH and is considered an objective measure of patient functional status. Subjects will be instructed to walk down a corridor at a comfortable speed as far as they can manage for six minutes. Distance <500 meters suggests considerable exercise limitation; Distance 500-800 meters suggests moderate limitation; Distance >800 meters

(with no rests) suggests mild or no limitation. Peak exposure 6MWD will occur by conducting 6-minute walk test (6MWT) within 10 to 60 minutes after the most recent dose of study drug dose.
[Time Frame: Baseline and Week 12]

2. Change in Trough 6-minute Walk Distance (6MWD) from Baseline to Week 15
The intent of the 6MWD test is to evaluate exercise capacity associated with carrying out activities of daily living. Change in 6MWD from Baseline to Week 15, correlates with the current clinical standard for assessing patient functional status in the treatment of PH and is considered an objective measure of patient functional status. Subjects will be instructed to walk down a corridor at a comfortable speed as far as they can manage for six minutes. Distance <500 meters suggests considerable exercise limitation; Distance 500-800 meters suggests moderate limitation; Distance >800 meters (with no rests) suggests mild or no limitation. Trough exposure 6MWD will occur by conducting 6-minute walk test (6MWT) at least four hours after the most recent study drug dose.
[Time Frame: Baseline and Week 15]

3. Change in plasma concentration of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) from Baseline to Week 16
The N-terminal pro-BNP (NT-proBNP) serum concentration is a useful biomarker associated with changes in right heart morphology and function. NT-proBNP serum concentration will be assessed to compare the severity of heart failure at Baseline and Week 16. Blood for NT-proBNP assessment must be drawn prior to conducting the 6-minute walk test (6MWT).
[Time Frame: Baseline and Week 16]

4. Change in Forced Expiratory Volume (FEV1) in One Second from Baseline to Week 16
Change in pulmonary function following inhaled treprostinil therapy will be measured by Forced Expiratory Volume in One Second (FEV1), the maximal amount of air forcefully exhaled in 1 second, calculated from a Pulmonary Function Test (PFT) performed at Baseline and Week 16.
[Time Frame: Baseline and Week 16]

5. Change in Forced Vital Capacity (FVC) from Baseline to Week 16
Change in pulmonary function following inhaled treprostinil therapy will be measured by Forced Vital Capacity (FVC), calculated from a Pulmonary Function Test (PFT) performed at Baseline and Week 16.
[Time Frame: Baseline and Week 16]

6. Change in Total Lung Capacity (TLC) from Baseline to Week 16
Change in pulmonary function following inhaled treprostinil therapy will be measured by Total Lung Capacity (TLC), calculated from a Pulmonary Function Test (PFT) performed at Baseline and Week 16.
[Time Frame: Baseline and Week 16]

7. Change in Lung Diffusion Capacity (DLCO) from Baseline to Week 16
Change in pulmonary function following inhaled treprostinil therapy will be measured by Lung Diffusion Capacity (DLCO), calculated from a Pulmonary Function Test (PFT) performed at Baseline and Week 16.
[Time Frame: Baseline and Week 16]

8. Incidence of Adverse Events Among Participants through 16 Weeks
The incidence of adverse events among participants throughout the 16 week study will be measured by the number of participants analyzed and the percentage of those participants who experienced an adverse event.
[Time Frame: 16 Weeks]

Eligibility

Minimum Age
18 Years

Maximum Age
79 Years

Sex

All

Gender-based Eligibility

Gender Eligibility Description

Accepts Healthy Volunteers

No

Criteria

Inclusion Criteria:

1. Subject voluntarily gives informed consent to participate in the study.
2. Males and females aged 18 - 79 years at the time of informed consent.

   a. Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will: i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or ii. Use two medically acceptable, highly-effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug.

   b. Males must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.

3. The subject has a confirmed diagnosis (based on computed tomography [CT] imaging and pulmonary function tests [PFTs] performed within six months prior to randomization) of World Health Organization (WHO) Group 3 PH associated with one of the following:

   a. Idiopathic interstitial pneumonia (IIP) including: i. Idiopathic pulmonary fibrosis (IPF) ii. Idiopathic nonspecific interstitial pneumonia iii. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) iv. Desquamative interstitial pneumonia (DIP) v. Cryptogenic organizing pneumonia (COP) vi. Acute interstitial pneumonitis (AIP) vii. Idiopathic lymphoid interstitial pneumonia viii. Idiopathic pleuroparenchymal fibroelastosis iix. Unclassifiable idiopathic interstitial pneumonia b. Chronic hypersensitivity pneumonitis (CHP) c. Occupational or environmental lung disease (drug or radiation-induced) d. Combined pulmonary fibrosis and emphysema (CPFE)

4. Subjects are required to have a right heart catheterization (RHC) within one year prior to randomization with the following documented parameters:

   1. Pulmonary vascular resistance (PVR) ≥ 4 Wood Units (WU) and
   2. A left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) of ≤ 12 mmHg if PVR ≥ 4 WU to < 6.25 WU or ≤ 15 mmHg if PVR ≥ 6.25 WU and
   3. A mean pulmonary arterial pressure (mPAP) of ≥ 30 mmHg
5. A baseline diffusing capacity of the lungs for carbon monoxide (DLCO) of < 50%
6. Baseline 6MWD ≥ 100 meters
7. The subject has not received any PAH approved therapy including: prostacyclin therapy (i.e., epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE-5I), or soluble guanylate cyclase stimulator (sGC) within 60 days of randomization.
8. Subjects on a chronic medication for underlying lung disease must be on a stable and optimized dose for ≥ 30 days prior to randomization. Subjects receiving pirfenidone or nintedanib must have been receiving treatment for at least 90 days and on a stable dose for at least 30 days prior to randomization.
9. Subjects on a supportive medication therapy (e.g., anticoagulants, diuretics, oxygen, etc.) must be on a stable and optimized dose for ≥ 30 days prior to randomization. Exceptions are the discontinuation or dose changes of anticoagulants and / or dose change of diuretics.

10. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

Exclusion criteria:

1. The subject has a diagnosis of pulmonary arterial hypertension (PAH) or PH for reasons other than ILD as outlined in inclusion criterion 3. This would include, but is not limited to, the concomitant presence of thromboembolic disease (acute or chronic), untreated or inadequately treated obstructive sleep apnea (OSA), connective tissue disease (including but not limited to systemic sclerosis, scleroderma, or systemic lupus erythematosus [SLE]), sarcoidosis, human immunodeficiency virus (HIV)-1 infection, portopulmonary hypertension, and other conditions of the WHO Group I, II, IV, and V classification.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any PAH approved therapy including: prostacyclin therapy (i.e., epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), ERA, PDE-5I, or sGC within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:

    1. LVEDP or PCWP > 15 mmHg (or > 12 mmHg if PVR ≥ 4 to < 6.25 WU)
    2. Left ventricular ejection fraction < 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography.

    Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) will not be excluded.

5. Subjects must not have three or more of the following left ventricular disease/dysfunction risk factors:

    1. Body Mass Index (BMI) ≥ 30 kg/m2
    2. History of Essential Hypertension
    3. Diabetes Mellitus - any type
    4. Historical evidence of significant coronary disease established by any one of the following:

    i. history of myocardial infarction or percutaneous coronary intervention or angiographic, or ii. evidence of coronary artery disease (> 50% stenosis in at least one coronary artery), or iii. positive stress test with imaging, or previous coronary artery bypass graft, or stable angina

6. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
7. Use of any inhaled tobacco/marijuana products or significant history of drug abuse within six months prior to randomization.
8. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization.
9. Initiation of pulmonary rehabilitation within 12 weeks prior to the randomization.
10. The subject has uncontrolled systemic hypertension as evidenced by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
11. The subject has any form of congenital heart disease or congenital heart defect (repaired or unrepaired) other than a patent foramen ovale (PFO).
12. The subject has anemia as defined by a screening hemoglobin value < 9.0 g/dL, active infection, or any other condition that would interfere with the interpretation of study assessments.
13. The subject has a Body Mass Index ≥ 40 kg/m2.
14. The subject has any musculoskeletal disorder (i.e., arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (i.e., cane or walker), or has any other condition that would limit ambulation.
15. Use of any investigational drug/device, or participation in any investigational study within 30 days prior to randomization.

Contacts/Locations

Central Contact Person

- Name
  Nicole Leedom

  Email
  nleedom@unither.com

- Name
  Hilary Mauney

  Email
  hmauney@unither.com

Study Officials

- Name
  Aaron Waxman, MD

  Role
  Principal Investigator

  Affiliation
  Brigham and Women's Hospital

Location

- **Birmingham, Alabama, United States, 35294**

  Status:
  Recruiting

  Facility:
  University of Alabama at Birmingham

  Contact:
  - Contact
    - Leigh Powell
    - 205-975-9859
    - lcpowell@uabmc.edu
  - Principal Investigator
    - Robert Bourge, MD

- **Phoenix, Arizona, United States, 85012**

  Status:
  Recruiting

  Facility:
  Arizona Pulmonary Specialists, Ltd.

  Contact:
  - Contact
    - Monya Pierce
    - 602-271-0832
    - monya-research@hotmail.com
  - Principal Investigator
    - Jeremy Feldman, MD

- **Tucson, Arizona, United States, 85724**

  Status:
  Recruiting

Facility:
University of Arizona

Contact:
- Contact
  - Stacey Palm
  - 520-626-8034
  - staceypalm@email.arizona.edu
- Principal Investigator
  - Franz Rischard, DO

- **Fresno, California, United States, 93701**

Status:
Recruiting

Facility:
University of California San Francisco - Fresno

Contact:
- Contact
  - Sonia Garcia
  - 559-499-6637
  - sgarcia@fresno.ucsf.edu
- Principal Investigator
  - Vijay Balasubramanian

- **Riverside, California, United States, 92505**

Status:
Recruiting

Facility:
Pacific Pulmonary Medical Group

Contact:
- Contact
  - Mostafa Elsiah
  - 951-373-5827
  - mostafa.ppmg@gmail.com
- Principal Investigator
  - Heba Ismail, MD

- **Sacramento, California, United States, 95817**

Status:
Recruiting

Facility:
University of California Davis Medical Center

Contact:
- Contact
  - Megan Suderow
  - 916-734-1554
  - mlsuderow@ucdavis.edu
- Principal Investigator
  - Roblee Allen

- **Aurora, Colorado, United States, 80045**

Status:
Recruiting

Facility:
University of Colorado Hospital - Cardiac and Vascular Center

Contact:

- Contact
  - Cheryl Abbott, RN, CCRP
  - 303-724-7466
  - cheryl.abbott@ucdenver.edu
- Principal Investigator
  - Todd Bull, MD

- **Denver, Colorado, United States, 80206**

  Status:
  Recruiting

  Facility:
  National Jewish Health

  Contact:
  - Contact
    - Carmen Egidio
    - 303-270-2622
    - egidioc@njhealth.org
  - Principal Investigator
    - Amy Olson, MD

- **Washington, District of Columbia, United States, 20007**

  Status:
  Recruiting

  Facility:
  Georgetown University Hospital

  Contact:
  - Contact
    - Michele Cooney
    - 202-444-0895
    - Cooneym@gunet.georgetown.edu
  - Principal Investigator
    - Tunay Kuru, MD

- **Clearwater, Florida, United States, 33765**

  Status:
  Recruiting

  Facility:
  St. Francis Sleep, Allergy and Lung Institute

  Contact:
  - Contact
    - Ellen Linden
    - 727-210-4606
    - elinden@stfrancismed.com
  - Principal Investigator
    - Francis Averill, MD

- **Jacksonville, Florida, United States, 32209**

  Status:
  Recruiting

  Facility:
  University of Florida College of Medicine, Jacksonville

  Contact:
  - Contact
    - Minal Patel

- 904-244-1106
- Minal.patel@jax.ufl.edu
- Principal Investigator
  - Vandana Seeram, MD

- **Miami, Florida, United States, 33136**

  Status:
  Recruiting

  Facility:
  University of Miami

  Contact:
  - Contact
    - Eliana Mendes, MD
  - Contact
    -
    - 305-243-2568
    - emendes@med.miami.edu
  - Principal Investigator
    - David De La Zerda, MD

- **Orlando, Florida, United States, 32803**

  Status:
  Recruiting

  Facility:
  Central Florida Pulmonary Group, P.A.

  Contact:
  - Contact
    - Zarah Rodriguez
    - 407-841-1100, 107
    - zrodriguez@cfpulmonary.com
  - Principal Investigator
    - Syed Mobin, MD

- **South Miami, Florida, United States, 33143**

  Status:
  Recruiting

  Facility:
  South Miami Heart Specialists

  Contact:
  - Contact
    - Jojie Calderin
    - 305-999-3301
    - gcalderin@ampmrc.com
  - Principal Investigator
    - Javier Jimenez, MD

- **Weston, Florida, United States, 33331**

  Status:
  Recruiting

  Facility:
  Cleveland Clinic Florida

  Contact:
  - Contact
    - Norma Jean Barton
    - 954-659-6213

- bartonn2@ccf.org
- Principal Investigator
  - Franck Rahaghi, MD
- **Atlanta, Georgia, United States, 30322**

  Status:
  Recruiting

  Facility:
  The Emory Clinic

  Contact:
  - Contact
    - Jane Gillespie, RN
  - Contact
    -
    - 404-712-8204
    - jane.gillespie@emory.edu
  - Principal Investigator
    - Micah Fisher, MD
- **Chicago, Illinois, United States, 60611**

  Status:
  Recruiting

  Facility:
  Northwestern University

  Contact:
  - Contact
    - Margaret Travis, RN, BSN
    - 312-695-2269
    - margaret.travis@northwestern.edu
  - Principal Investigator
    - Hector Cajigas, MD
- **Chicago, Illinois, United States, 60612**

  Status:
  Recruiting

  Facility:
  University of Illinois at Chicago Hospital

  Contact:
  - Contact
    - Adam Ostrower
    - 312-355-5934
    - ostrower@uic.edu
  - Principal Investigator
    - Roberto Machado, MD
- **Chicago, Illinois, United States, 60637**

  Status:
  Recruiting

  Facility:
  University of Chicago Medical Center

  Contact:
  - Contact
    - Sandy Coslet
  - Contact
    -

        - 773-864-5768
        - scoslet@medicine.bsd.uchicago.edu
    - Principal Investigator
        - Remzi Bag, MD
- **Maywood, Illinois, United States, 60153**

  Status:
  Recruiting

  Facility:
  Loyola University Medical Center

  Contact:
    - Contact
        - Jessica Shore
        - 708-216-2027
        - jshore@luc.edu
    - Principal Investigator
        - James Gagermeier, MD
- **Indianapolis, Indiana, United States, 46202**

  Status:
  Recruiting

  Facility:
  IU Health Physicians Advanced Heart & Lung Clinic

  Contact:
    - Contact
        - Erin Turk
        - 317-962-3183
        - eturk@iuhealth.org
    - Principal Investigator
        - William Harvey, MD
- **Indianapolis, Indiana, United States, 46250**

  Status:
  Recruiting

  Facility:
  Community Heart and Vascular Hospital

  Contact:
    - Contact
        - Joanna Greene-Nashold, RN
        - 317-621-8629
        - jgnashold@ecommunity.com
    - Principal Investigator
        - Navneet Lather, MD
- **Indianapolis, Indiana, United States, 46260**

  Status:
  Recruiting

  Facility:
  St. Vincent Medical Group, Inc.

  Contact:
    - Contact
        - Regina Margiotti
        - 317-338-6151
        - ramargio@stvincent.org
    - Principal Investigator

- Ashwin Ravichandran, MD

- **Kansas City, Kansas, United States, 66160**

  Status:
  Recruiting

  Facility:
  University of Kansas Medical Center

  Contact:
  - Contact
    - Mia Zou
    - 913-588-7117
    - mzou@kumc.edu
  - Principal Investigator
    - Leslie Spikes, MD

- **Lexington, Kentucky, United States, 40536**

  Status:
  Recruiting

  Facility:
  University of Kentucky Medical Center

  Contact:
  - Contact
    - April Butler
  - Contact
    -
    - 859-218-6740
    - april.evans@uky.edu
  - Principal Investigator
    - Ketan Buch, MD

- **Louisville, Kentucky, United States, 40202**

  Status:
  Recruiting

  Facility:
  Kentuckiana Pulmonary Associates

  Contact:
  - Contact
    - Martha Royse, APRN
    - 502-587-8000
    - roysenp@gmail.com
  - Principal Investigator
    - John McConnell, MD

- **Louisville, Kentucky, United States, 40202**

  Status:
  Recruiting

  Facility:
  University of Louisville Physicians Outpatient Center

  Contact:
  - Contact
    - Joan Hamlyn
    - 502-852-8739
    - Joan.hamlyn@louisville.edu
  - Principal Investigator
    - Jimmy Shaun Smith, DO

- **New Orleans, Louisiana, United States, 70112**

  Status:
  Recruiting

  Facility:
  Louisiana State University Health Sciences Center New Orleans

  Contact:
  - Contact
    - Paula Lauto, RN
    - 504-568-3451
    - plauto@lsuhsc.edu
  - Principal Investigator
    - Matthew Lammi, MD

- **New Orleans, Louisiana, United States, 70112**

  Status:
  Recruiting

  Facility:
  Tulane University

  Contact:
  - Contact
    - Sandy Ditta
    - 504-988-4040
    - sditta@tulane.edu
  - Principal Investigator
    - Shigeki Saito, MD

- **Baltimore, Maryland, United States, 21202**

  Status:
  Recruiting

  Facility:
  University of Maryland Medical Center

  Contact:
  - Contact
    - Lioubov Poliakova
    - 410-328-6885
    - lpoliako@medicine.umaryland.edu
  - Principal Investigator
    - Gautam V. Ramani, MD

- **Boston, Massachusetts, United States, 02111**

  Status:
  Recruiting

  Facility:
  Tufts Medical Center

  Contact:
  - Contact
    - Karen Visnaw, RN
    - 617-636-1334
    - Kvisnaw@tuftsmedicalcenter.org
  - Principal Investigator
    - Nicholas Hill, MD

- **Boston, Massachusetts, United States, 02115**

  Status:

Recruiting

Facility:
Brigham & Women's Hospital

Contact:
- Contact
  - Laurie Lawler, RN
  - 617-525-9731
  - llawler@partners.org
- Principal Investigator
  - Aaron B. Waxman, MD

- **Detroit, Michigan, United States, 48202**

  Status:
  Recruiting

  Facility:
  Henry Ford Health System

  Contact:
  - Contact
    - Jackie Day
    - 313-916-1254
    - jday5@hfhs.org
  - Principal Investigator
    - Rana Awdish, MD

- **Grand Rapids, Michigan, United States, 49503**

  Status:
  Recruiting

  Facility:
  Spectrum Health Medical Center

  Contact:
  - Contact
    - Molly Cope, RN
    - 616-391-3869
    - molly.cope@spectrumhealth.org
  - Principal Investigator
    - Reda Girgis, MD

- **Minneapolis, Minnesota, United States, 55455**

  Status:
  Not yet recruiting

  Facility:
  University of Minnesota

  Contact:
  - Contact
    - Gretchen Peichel
    - 612-626-6237
    - gpeichel@umn.edu
  - Principal Investigator
    - Thenappan Thenappan, MD

- **Omaha, Nebraska, United States, 68198**

  Status:
  Recruiting

  Facility:

University of Nebraska Medical Center

Contact:

- Contact
  - Traci Nelson
  - 402-559-7585
  - trnelson@unmc.edu
- Principal Investigator
  - Austin Thompson, MD

- **Albuquerque, New Mexico, United States, 87131**

  Status:
  Recruiting

  Facility:
  The University of New Mexico

  Contact:
  - Contact
    - Barbara Butcher, PhD, BSN, RN
    - 505-925-1160
    - BButcher@salud.unm.edu
  - Principal Investigator
    - Lana Melendres-Groves, MD

- **Albany, New York, United States, 12208**

  Status:
  Recruiting

  Facility:
  Albany Medical College

  Contact:
  - Contact
    - Furqan Ilyas
    - 518-262-1542
    - ilyasf@mail.amc.edu
  - Principal Investigator
    - Boris Medarov, MD

- **Brooklyn, New York, United States, 11215**

  Status:
  Recruiting

  Facility:
  New York Methodist Hospital

  Contact:
  - Contact
    - Puja Chadha
    - 718-780-5614
    - puc9004@nyp.org
  - Principal Investigator
    - Ruth Minkin, MD

- **Fayetteville, New York, United States, 13066**

  Status:
  Recruiting

  Facility:
  Pulmonary Health Physicians, PC

  Contact:

- Contact
  - Victoria Gabris, RN
- Contact
  -
  - 315-234-0816
  - Victoria.Gabris@CNYLungs.com
- Principal Investigator
  - Sherif El Bayadi, MD

- **Mineola, New York, United States, 11501**

  Status:
  Recruiting

  Facility:
  Winthrop University Hospital

  Contact:
  - Contact
    - Kimberly Byrnes
    - 516-663-9582
    - kbyrnes@winthrop.org
  - Principal Investigator
    - Shilpa DeSouza, MD

- **New Hyde Park, New York, United States, 11040**

  Status:
  Recruiting

  Facility:
  Northwell Health

  Contact:
  - Contact
    - Sameer Verma, MD
    - 516-465-5437
    - SVerma3@northwell.edu
  - Principal Investigator
    - Arunabh Talwar, MD

- **New York, New York, United States, 10003**

  Status:
  Recruiting

  Facility:
  ICAHN School of Medicine - Mount Sinai Beth Israel

  Contact:
  - Contact
    - Anabela Barroso
    - 212-844-8824
    - abarroso@CHPNET.ORG
  - Principal Investigator
    - Roxana Sulica, MD

- **New York, New York, United States, 10029**

  Status:
  Recruiting

  Facility:
  The Mount Sinai Hospital

  Contact:
  - Contact

- Ewelina Wojtaszek
- Contact
  -
  - 917-501-5255
  - ewelina.wojtaszek@mountsinai.org
- Principal Investigator
  - Radha Gopalan, MD

- **Chapel Hill, North Carolina, United States, 27599**

  Status:
  Recruiting

  Facility:
  University of North Carolina at Chapel Hill

  Contact:
  - Contact
    - Dakota Buhrman
    - 919-445-0353
    - dakota_buhrman@med.unc.edu
  - Principal Investigator
    - Hubert James (Jimmy) Ford III, MD

- **Cincinnati, Ohio, United States, 45219**

  Status:
  Recruiting

  Facility:
  The Carl and Edyth Lindner Research Center at The Christ Hospital

  Contact:
  - Contact
    - Christine Lawrence
    - 513-585-1777
    - christine.lawrence@thechristhospital.com
  - Principal Investigator
    - Peter Engel, MD

- **Cincinnati, Ohio, United States, 45267**

  Status:
  Recruiting

  Facility:
  University of Cincinnati Health

  Contact:
  - Contact
    - Tammy Roads
    - 513-558-2148
    - roadst@ucmail.uc.edu
  - Principal Investigator
    - Jean Elwing, MD

- **Cleveland, Ohio, United States, 44106**

  Status:
  Recruiting

  Facility:
  University Hospitals Cleveland Medical Center

  Contact:
  - Contact
    - Mary Andrews

- mary.andrews@uhhospitals.org
- Contact
  -
  - 216-844-2386
- Principal Investigator
  - Robert Schilz, DO

- **Oklahoma City, Oklahoma, United States, 73104**

  Status:
  Recruiting

  Facility:
  The University of Oklahoma Health Sciences Center (OUHSC)

  Contact:
  - Contact
    - Jennifer Robertson
    - 405-271-6173
    - jennifer-robertson@ouhsc.edu
  - Principal Investigator
    - Himanshu Bhardwaj, MD

- **Lancaster, Pennsylvania, United States, 17603**

  Status:
  Recruiting

  Facility:
  Lancaster General Health

  Contact:
  - Contact
    - Lou Anne Kruse, RN, BSN
    - 717-544-1777
    - lakruse@LGHealth.org
  - Principal Investigator
    - Justin Roberts, DO

- **Philadelphia, Pennsylvania, United States, 19140**

  Status:
  Recruiting

  Facility:
  Temple University Hospital

  Contact:
  - Contact
    - Gayle Jones, RN
    - 215-707-1041
    - Gayle.Jones@tuhs.temple.edu
  - Principal Investigator
    - Sheila Weaver, DO

- **Pittsburgh, Pennsylvania, United States, 15212**

  Status:
  Not yet recruiting

  Facility:
  Allegheny General Hospital

  Contact:
  - Contact
    - Joan Rossi, RN
    - 412-359-3293

- joan.rossi@ahn.org
- Principal Investigator
  - Amresh Raina, MD

- **Pittsburgh, Pennsylvania, United States, 15213**

  Status:
  Recruiting

  Facility:
  University of Pittsburgh Medical Center

  Contact:
  - Contact
    - Swati Gulati
    - 412-864-6371
    - gulatis2@upmc.edu
  - Principal Investigator
    - Michael Risbano

- **Anderson, South Carolina, United States, 29621**

  Status:
  Recruiting

  Facility:
  AnMed Health Pulmonary and Sleep Medicine

  Contact:
  - Contact
    - Charlesa Davis
    - 864-512-8519
    - charlesa.davis2@anmedhealth.org
  - Principal Investigator
    - Abhijit Raval, MD

- **Charleston, South Carolina, United States, 29425**

  Status:
  Recruiting

  Facility:
  Medical University of South Carolina

  Contact:
  - Contact
    - Robyn Do
    - 843-792-1221
    - dorobyn@musc.edu
  - Principal Investigator
    - Rahul Argula, MD

- **Knoxville, Tennessee, United States, 37909**

  Status:
  Recruiting

  Facility:
  Statcare Pulmonary Consultants

  Contact:
  - Contact
    - Krista Tibbs
    - 865-934-2676
    - ktibbs@biomed-research.com
  - Principal Investigator
    - John Swisher, MD

- **Dallas, Texas, United States, 75390**

  Status:
  Recruiting

  Facility:
  UT Southwestern Medical Center

  Contact:
  - Contact
    - Adetoun Sodimu
    - 214-645-6439
    - Adetoun.Sodimu@UTSouthwestern.edu
  - Principal Investigator
    - Sonja Bartolome, MD

- **Houston, Texas, United States, 77030**

  Status:
  Recruiting

  Facility:
  Houston Methodist

  Contact:
  - Contact
    - Ann Saulino, RN
    - 713-441-7182
    - asaulino@houstonmethodist.org
  - Principal Investigator
    - Adaani Frost, MD

- **Houston, Texas, United States, 77030**

  Status:
  Recruiting

  Facility:
  Michael E. DeBakey VA Medical Center

  Contact:
  - Contact
    - Sarah Perusich
    - 713-794-7294
    - Sarah.Perusich@va.gov
  - Principal Investigator
    - Lavannya Pandit, MD

- **Houston, Texas, United States, 77030**

  Status:
  Recruiting

  Facility:
  The University of Texas Health Science Center at Houston

  Contact:
  - Contact
    - Tiffany Ostovar-Kermani
    - 713-500-6851
    - Tiffany.G.OstovarKermani@uth.tmc.edu
  - Principal Investigator
    - Bela Patel, MD

- **San Antonio, Texas, United States, 78229**

  Status:

Not yet recruiting

Facility:
The University of Texas Health Science Center at San Antonio

Contact:
- Contact
  - Olga Dib
  - 210-415-1180
  - Dibo@uthscsa.edu
- Principal Investigator
  - Deborah Levine, MD

- **Temple, Texas, United States, 76508**

Status:
Recruiting

Facility:
Scott & White Memorial Hospital

Contact:
- Contact
  - Lori Murdoch
  - 254-724-7168
  - Lori.Murdoch@BSWHealth.org
- Principal Investigator
  - Peter Yau, MD

- **Colchester, Vermont, United States, 05446**

Status:
Recruiting

Facility:
University of Vermont, Vermont Lung Center

Contact:
- Contact
  - Kathy Meehan
  - 802-847-3627
  - Kathy.Meehan@uvmhealth.org
- Principal Investigator
  - Maryellen Antkowiak, MD

- **Norfolk, Virginia, United States, 23507**

Status:
Recruiting

Facility:
Sentara Cardiovascular Research Institute

Contact:
- Contact
  - Melinda Bullivant
  - 757-388-4024
  - MMBULLIV@sentara.com
- Principal Investigator
  - Michael Eggert

- **Richmond, Virginia, United States, 23229**

Status:
Recruiting

Facility:

Pulmonary Associates of Richmond

Contact:

- Contact
  - Rose Sidell
  - 804-288-5945
  - rsidell@paraccess.com
- Principal Investigator
  - Shilpa Johri, MD

- **Madison, Wisconsin, United States, 53792**

Status:
Recruiting

Facility:
University of Wisconsin School of Medicine and Public Health

Contact:

- Contact
  - Lori Wollet
  - 608-263-0524
  - ljwollet@medicine.wisc.edu
- Principal Investigator
  - James Runo, MD

- **Milwaukee, Wisconsin, United States, 53215**

Status:
Recruiting

Facility:
Aurora St. Luke's Medical Center

Contact:

- Contact
  - Linda Boehm, RN
  - 414-649-5664
  - linda.boehm@aurora.org
- Principal Investigator
  - Dianne Zwicke, MD

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References

Citations

Links

Document Section

EXHIBIT 20

Inhaled Treprostinil and FVC Change in Patients With Interstitial Lung Disease and Associated Pulmonary Hypertension

Article *in* SSRN Electronic Journal · January 2021

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Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study

Steven D Nathan, Aaron Waxman, Sudarshan Rajagopal, Amy Case, Shilpa Johri, Hilary DuBrock, David J De La Zerda, Sandeep Sahay, Christopher King, Lana Melendres-Groves, Peter Smith, Eric Shen, Lisa D Edwards, Andrew Nelsen, Victor F Tapson

Summary

Background **INCREASE was a randomised, placebo-controlled, phase 3 trial that evaluated inhaled treprostinil in patients with interstitial lung disease (ILD) and associated pulmonary hypertension. Treprostinil improved exercise capacity from baseline to week 16, assessed with the use of a 6-min walk test, compared with placebo. Improvements in forced vital capacity (FVC) were also reported. The aim of this post-hoc analysis was to further characterise the effects of inhaled treprostinil on FVC in the overall study population and in various subgroups of interest.**

Methods **In this post-hoc analysis, we evaluated FVC changes in the overall study population and in various subgroups defined by cause of disease or baseline clinical parameters. The study population included patients aged 18 years and older who had a diagnosis of ILD based on evidence of diffuse parenchymal lung disease on chest CT done within 6 months before random assignment (not centrally adjudicated). All analyses were done on the intention-to-treat population, defined as individuals who were randomly assigned and received at least one dose of study drug. The INCREASE study is registered with ClinicalTrials.gov, NCT02630316.**

Findings **Between Feb 3, 2017, and Aug 30, 2019, 326 patients were enrolled in the INCREASE trial. Inhaled treprostinil was associated with a placebo-corrected least squares mean improvement in FVC of 28·5 mL (SE 30·1; 95% CI –30·8 to 87·7; p=0·35) at week 8 and 44·4 mL (35·4; –25·2 to 114·0; p=0·21) at week 16, with associated percentage of predicted FVC improvements of 1·8% (0·7; 0·4 to 3·2; p=0·014) and 1·8% (0·8; 0·2 to 3·4; p=0·028). Subgroup analysis of patients with idiopathic interstitial pneumonia showed FVC differences of 46·5 mL (SE 39·9; 95% CI –32·5 to 125·5; p=0·25) at week 8 and 108·2 mL (46·9; 15·3 to 201·1; p=0·023) at week 16. Analysis of patients with idiopathic pulmonary fibrosis showed FVC differences of 84·5 mL (52·7; –20·4 to 189·5; p=0·11) at week 8 and 168·5 mL (64·5; 40·1 to 297·0; p=0·011) at week 16. The most frequent adverse events included cough, headache, dyspnoea, dizziness, nausea, fatigue, and diarrhoea.**

Interpretation **In patients with ILD and associated pulmonary hypertension, inhaled treprostinil was associated with improvements in FVC versus placebo at 16 weeks. This difference was most evident in patients with idiopathic interstitial pneumonia, particularly idiopathic pulmonary fibrosis. Inhaled treprostinil appears to be a promising therapy for idiopathic pulmonary fibrosis that warrants further investigation in a prospective, randomised, placebo-controlled study.**

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Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA, USA (Prof S D Nathan MD, C King MD); **Pulmonary and Critical Care Medicine, Department of Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA** (A Waxman MD); **Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, NC, USA** (S Rajagopal MD); **Piedmont Healthcare, Austell, GA, USA** (A Case MD); **Pulmonary Associates of Richmond, Richmond, VA, USA** (S Johri MD); **Department of Internal Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN, USA** (H DuBrock MD); **Division of Pulmonary & Critical Care Medicine, University of Miami Health System, Miami, FL, USA** (D J De La Zerda MD); **Division of Pulmonary, Critical Care and Sleep Medicine, Houston Methodist Hospital, Houston, TX, USA** (S Sahay MD); **Pulmonary & Critical Care Division, University of New Mexico, 1 University of New Mexico, DoIM MSC10-5550, Albuquerque, NM, USA** (L Melendres-Groves MD); **United Therapeutics Corporation, Research Triangle Park, NC, USA** (P Smith PharmD, E Shen PharmD, L D Edwards PhD, A Nelsen PharmD); **Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA** (Prof V F Tapson MD)

Introduction

Interstitial lung diseases (ILDs) encompass a broad range of conditions that are categorised by varying amounts of inflammation and fibrosis. Idiopathic interstitial pneumonias are a category of ILD, of which idiopathic pulmonary fibrosis is the most common form.[1] Clinical trials of idiopathic pulmonary fibrosis treatments have resulted in approval in many countries of two so-called antifibrotic agents, pirfenidone and nintedanib.[2,3,4] Both drugs have been shown to slow loss of lung function, as measured by forced vital capacity (FVC). Results of clinical trials for both drugs in other forms of fibrotic lung disease—including scleroderma-associated ILD, ILDs characterised by progressive fibrosis, and unclassifiable ILD—indicate that both agents have antifibrotic effects beyond idiopathic pulmonary fibrosis.[5,6,7] These results suggest that once lung fibrosis supervenes, there are pathways common to various forms of ILD that might be targets for therapy.

Treprostinil is a stable analogue of prostacyclin, which promotes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.[8] The inhaled formulation of treprostinil is approved in the USA for the treatment of WHO group 1 pulmonary hypertension.[8,9] In addition to its effects on the pulmonary vasculature, there are data to suggest that treprostinil has antifibrotic properties. Specifically, treprostinil has been shown to affect extracellular matrix

Correspondence to:
Prof Steven D Nathan, Advanced Lung Disease and Lung Transplant Program, Falls Church, VA 22042, USA
steven.nathan@inova.org

Research in context

Evidence before this study

Clinical trials in patients with chronic fibrosing interstitial lung diseases (ILDs) have led to the development of two antifibrotic agents, nintedanib and pirfenidone. These therapies have been shown to reduce the rate of decline in lung function and are now recommended in clinical practice guidelines for patients with idiopathic pulmonary fibrosis. The INCREASE study was a randomised clinical trial of patients with ILD and pulmonary hypertension that evaluated the safety and efficacy of inhaled treprostinil. The study met its primary endpoint of change in the peak 6-min walk distance at week 16. Pulmonary function testing was obtained as a safety parameter in this study. Somewhat unexpectedly, this study also showed that inhaled treprostinil was associated with improvements in forced vital capacity (FVC) over a 16-week period. We searched PubMed on June 9, 2021, using the search terms "treprostinil" and "lung function" for all articles published from database inception up to June 9, 2021, with no language restrictions. One retrospective study of 22 patients with interstitial lung disease and associated pulmonary hypertension treated with inhaled treprostinil assessed lung function. No significant changes were observed in percentage predicted FVC but this study was limited by its observational, uncontrolled design. The effects of inhaled treprostinil on lung function in this disease population have otherwise not been studied.

Added value of this study

In this post-hoc analysis of the INCREASE trial, inhaled treprostinil was associated with significant improvements in the percentage of predicted FVC at week 8 and week 16. Improvement in FVC was greatest among patients with idiopathic interstitial pneumonia, particularly those with idiopathic pulmonary fibrosis. These results suggest that inhaled treprostinil might have independent antifibrotic properties beyond traditional vasodilatory effects. Whether this will be substantiated in a study of patients with interstitial lung disease, with or without pulmonary hypertension, remains to be determined.

Implications of all the available evidence

The present study serves as proof of concept that inhaled treprostinil can have a beneficial effect on the loss of lung function in patients with ILDs and associated pulmonary hypertension. These findings were most pronounced in patients with idiopathic pulmonary fibrosis. Further studies are needed to investigate the clinical benefits of inhaled treprostinil in this patient population, with or without associated pulmonary hypertension, and to explore potential mechanisms of action.

remodelling and fibrosis in vitro by reducing recruitment of fibrocytes to sites of vascular remodelling, as well as suppressing profibrotic fibroblast activity and the synthesis and deposition of collagen and fibronectin in mice.[10,11]

The INCREASE study was a 16-week randomised controlled trial that was designed to evaluate the safety and efficacy of inhaled treprostinil in patients with ILD and pulmonary hypertension documented by right heart catheterisation. Patients received inhaled treprostinil, up to 12 breaths (72 µg) four times daily, or placebo.[12] The dose of drug or placebo was adjusted, with dose escalation (an additional breath, four times daily) occurring as often as every 3 days, with a target dose of nine breaths four times daily and a maximum dose of 12 breaths four times daily. Investigators adjusted the dose for each individual patient to achieve the maximum tolerated dose. The study met its primary endpoint of change in the peak 6-min walk distance, a measure of exercise capacity, at week 16. Secondary endpoints, including change in N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration at week 16 and time to clinical worsening, were also met. Pulmonary function testing was done as a safety assessment at baseline, week 8, and week 16, and was previously reported.[12]

The aim of this post-hoc analysis was to further characterise the effects of inhaled treprostinil on FVC among the overall study population and in various subgroups of interest, including specific disease subgroups and patients stratified by median baseline clinical characteristics.

Methods

Study design and participants

INCREASE was a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. The steering committee in collaboration with the sponsor (United Therapeutics Corporation) designed the study and oversaw its conduct. Detailed study procedures and results have been described previously.[12] The study population included patients aged 18 years and older with a diagnosis of ILD based on evidence of diffuse parenchymal lung disease on chest CT done within 6 months before random assignment (not centrally adjudicated). Confirmation of WHO group 3 pulmonary hypertension was required, based on right heart catheterisation within 1 year before random assignment (including pulmonary vascular resistance >3 Wood units, pulmonary capillary wedge pressure ≤15 mm Hg, and mean pulmonary arterial pressure ≥25 mm Hg). Patients with connective tissue disease-associated ILD were additionally required to have a baseline FVC <70%. Patients were randomly assigned (1:1) to inhaled treprostinil (Tyvaso; United Therapeutics Corporation, Research Triangle Park, NC, USA) or placebo in a double-blind manner. No new antifibrotics or anti-inflammatory

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	Idiopathic interstitial pneumonia including idiopathic pulmonary fibrosis (n=146)	Idiopathic pulmonary fibrosis only (n=92)	Combined pulmonary fibrosis and emphysema (n=82)	Connective tissue disease-associated ILD (n=72)	p value*
Sex	..	..	..	..	<0·0001
Female	60 (41%)	31 (34%)	23 (28%)	55 (76%)	..
Male	86 (59%)	61 (66%)	59 (72%)	17 (24%)	..
Age, years	67·8 (11·2)	70·8 (9·1)	71·7 (9·8)	57·2 (11·5)	..
Age group, years	..	..	..	..	<0·0001
<65	41 (28%)	15 (16%)	12 (15%)	53 (74%)	..
65 to <80	93 (64%)	67 (73%)	54 (66%)	19 (26%)	..
≥80	12 (8%)	10 (11%)	16 (20%)	0	..
Race	..	..	..	..	<0·0001
White	113 (77%)	76 (83%)	69 (84%)	34 (47%)	..
Black	24 (16%)	10 (11%)	12 (15%)	32 (44%)	..
American Indian or Alaska Native	2 (1%)	2 (2%)	0	1 (1%)	..
Asian	6 (4%)	4 (4%)	1 (1%)	4 (6%)	..
Multiple	0	0	0	1 (1%)	..
Unknown	1 (1%)	0	0	0	..
Ethnicity†	..	..	..	..	0·35
Hispanic or Latino	14 (10%)	10 (11%)	4 (5%)	8 (11%)	..
Not Hispanic or Latino	132 (90%)	82 (89%)	77 (95%)	64 (89%)	..
Time since diagnosis, years	0·6 (1·58)	0·5 (1·52)	0·4 (0·63)	0·6 (1·15)	0·59
Use of supplemental oxygen	102 (70%)	68 (74%)	64 (78%)	44 (61%)	0·073
Use of background therapy	..	..	..	..	<0·0001
None	91 (62%)	43 (47%)	69 (84%)	69 (96%)	..
Pirfenidone only	34 (23%)	30 (33%)	6 (7%)	2 (3%)	.
Nintedanib only	21 (14%)	19 (21%)	7 (9%)	1 (1%)	.
Pulmonary function tests					
Total lung capacity % predicted, %	60·7 (16·1)	60·2 (16·0)	77·8 (14·7)	52·9 (13·5)	<0·0001
Total lung capacity, L	3·6 (1·2)	3·7 (1·1)	4·8 (1·2)	2·9 (1·2)	<0·0001
FVC% predicted, %	59·5 (17·2)	60·8 (17·7)	82·5 (18·8)	49·5 (13·4)	<0·0001
FVC, mL	2175·7 (764·6)	2192·1 (724·6)	2992·6 (799·8)	1630·6 (552·4)	<0·0001
FEV_1% predicted, %	64·3 (19·0)	67·4 (18·8)	77·0 (21·1)	51·0 (15·1)	<0·0001
FEV_1, mL	1757·0 (585·8)	1793·1 (551·4)	2051·1 (598·6)	1320·1 (456·2)	<0·0001
DLCO% predicted, %	30·0 (12·1)	29·1 (11·5)	27·6 (11·3)	28·3 (11·7)	0·35
DLCO, mL/min/mm Hg	8·2 (4·6)	8·0 (4·7)	6·9 (3·0)	7·0 (4·0)	0·058

Data are n (%) or mean (SD). DLCO=diffusing capacity for carbon monoxide. FVC=forced vital capacity. ILD=interstitial lung disease. *p value compares idiopathic interstitial pneumonia including idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, and connective tissue disease populations only. †One patient in the placebo group had a missing response for ethnicity.

Table 1: **Baseline characteristics by disease cause**

therapies could be started during the study. The protocol was approved by the institutional review board at each participating site; all participants provided written informed consent.

Procedures and outcomes

This post-hoc analysis assessed the results of pulmonary function testing, which was prespecified as a safety endpoint and done at baseline, week 8, and week 16 (or at early termination) after sufficient recovery from the 6-min walk tests. Pulmonary function tests were done locally at each study site. We evaluated pulmonary function testing for the overall study population and by subgroup based on disease cause (idiopathic interstitial pneumonia [including idiopathic pulmonary fibrosis], idiopathic pulmonary fibrosis alone, combined pulmonary fibrosis and emphysema, and connective tissue disease-associated ILD) and subgroups stratified by median baseline characteristics (percentage of predicted FVC, percentage of predicted diffusing capacity for carbon monoxide [DLCO], pulmonary vascular resistance, mean pulmonary arterial pressure, NT-proBNP concentration, and 6-min

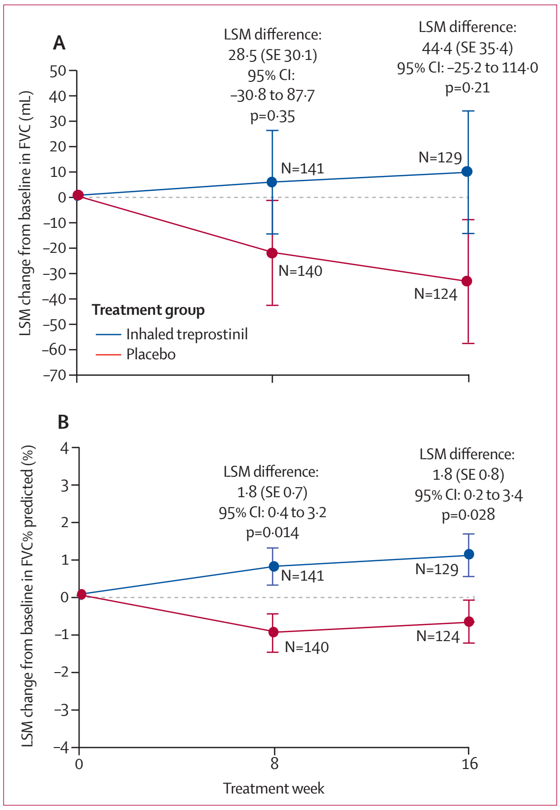

Figure 1: **Change in FVC at week 8 and week 16 for the overall population**
(A) LSM change in FVC (mL) by week for the overall intention-to-treat population. (B) LSM change in percentage of predicted FVC by week for the overall intention-to-treat population. Bars above and below the dots represent the SE. Mixed model repeated measures methodology was used to compare differences between the inhaled treprostinil and placebo group. FVC=forced vital capacity. LSM=least squares mean.

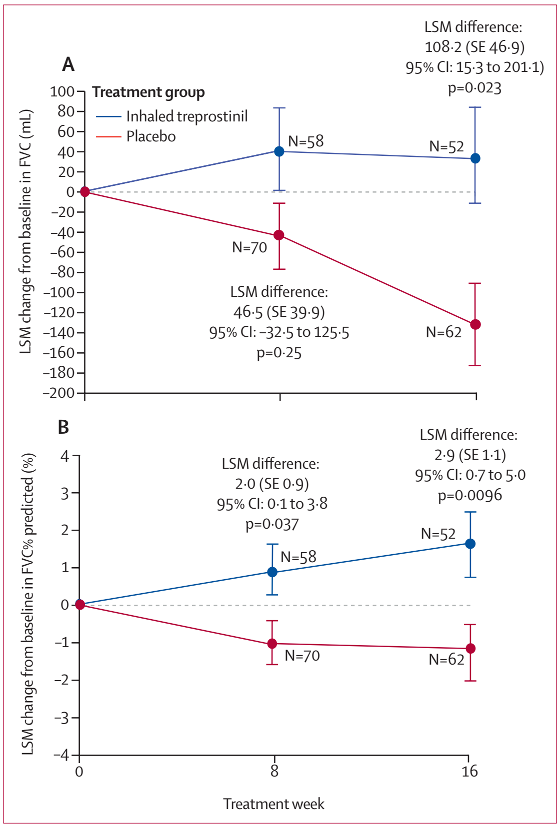

Figure 2: **Change in FVC at week 8 and week 16 for patients with idiopathic interstitial pneumonia**
(A) LSM change in FVC (mL) by week for the subgroup of patients with idiopathic interstitial pneumonia who received treprostinil or placebo. (B) LSM change in percentage of predicted FVC by week for the subgroup of patients with idiopathic interstitial pneumonia. Bars above and below the dots represent the SE. Mixed model repeated measures methodology was used to compare differences between the inhaled treprostinil and placebo group. FVC=forced vital capacity. LSM=least squares mean.

walk distance). An additional safety endpoint was the incidence of acute exacerbations of disease, determined by individual site principal investigators. Other prespecified safety endpoints (not included in the present analysis) were adverse events, oxygenation measured by pulse oximetry and supplemental oxygen requirement, clinical laboratory parameters, vital signs, electrocardiograms, and cardiopulmonary hospitalisations.[12]

Statistical analysis

The analyses reported here were post-hoc and exploratory. All assessments are summarised by descriptive statistics, as appropriate. Comparisons for categorical assessments were done by Mantel-Haenszel tests and comparisons for continuous assessments were done by Mann-Whitney tests. All analyses were done on the intention-to-treat population, defined as individuals who were randomly assigned and received at least one dose of study drug. The change in FVC was analysed using mixed model repeated measures (MMRM) methodology. The MMRM model included the change from baseline in FVC as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and baseline FVC as a covariate. An unstructured variance or covariance structure shared across treatment groups was used to model the within-subject errors. Treatment differences, associated 95% CIs, and p values were calculated. Change in percentage of predicted FVC was analysed similarly using the MMRM model, with the percentage of predicted FVC as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and baseline percentage of predicted FVC as a covariate. An unstructured variance or covariance structure shared across treatment groups was used to model the within-subject errors. Changes during the 16-week study were evaluated for the entire cohort and for disease-specific subgroups. Only observed data were included in the analysis; no data were imputed. When stratifying by baseline characteristics, median values were used as a cutoff (eg, below *vs* above median). The time to first acute exacerbation was analysed via Kaplan-Meier curves and log-rank test. $p<0.05$ was considered to indicate

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a statistically significant difference and no adjustments were made for multiplicity because this was an unplanned, post-hoc analysis. Analyses were done with SAS version 9.4. The INCREASE study is registered with ClinicalTrials.gov, NCT02630316.

Role of the funding source

In collaboration with the authors, the funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Feb 3, 2017, and Aug 30, 2019, 326 patients were enrolled in the INCREASE trial. Reasons for screen failures, baseline characteristics by treatment assignment, and study discontinuations have been described previously.[12] 146 (45%) of 326 patients had idiopathic interstitial pneumonia, of whom 92 (28%) had idiopathic pulmonary fibrosis, 37 (11%) had non-specific interstitial pneumonia, and 13 (4%) had unclassified idiopathic interstitial pneumonia. 82 (25%) of 326 patients had combined pulmonary fibrosis and emphysema, and 72 (22%) patients had connective tissue disease-associated ILD. 19 (6%) of 326 patients had chronic hypersensitivity pneumonitis, six (2%) had occupational lung disease, and one (<1%) had other idiopathic interstitial pneumonia. Demographic details of the four largest groups—idiopathic interstitial pneumonia (including idiopathic pulmonary fibrosis), idiopathic pulmonary fibrosis alone, combined pulmonary fibrosis and emphysema, and connective tissue disease-associated ILD—are shown in table 1. Notable differences included variable baseline pulmonary function tests between disease subtypes and younger age of patients with connective tissue disease-associated ILD. Anti-fibrotic therapy was most prevalent in patients with idiopathic pulmonary fibrosis, with 19 (21%) of 92 patients on nintedanib and 30 (33%) patients on pirfenidone. Baseline pulmonary function tests, haemodynamics, 6-min walk distance, NT-proBNP concentration, and St George's Respiratory Questionnaire data by disease group and treatment assignment are shown in the appendix (p 2).

In the inhaled treprostinil group, a median of ten breaths (IQR 8·5–12) and 12 breaths (9–12), corresponding to 66 μg and 72 μg per session, was achieved at week 8 and week 16, respectively, with 67 (51%) of 132 patients at week 8 and 67 (58%) of 116 patients at week 16 achieving 10–12 breaths (60–72 μg). 40 (25%) of 163 patients in the inhaled treprostinil group and 38 (23%) of 163 patients in the placebo group discontinued study drug prematurely but were encouraged to remain in the study and complete study assessments up to week 16. 33 patients assigned to inhaled treprostinil and 35 assigned to placebo discontinued study participation.[12]

Inhaled treprostinil was associated with a non-significant increase in placebo-corrected (the treatment difference between inhaled treprostinil and placebo) least squares mean FVC of 28·5 mL (SE 30·1; 95% CI –30·8 to 87·7; p=0·35) at week 8 and 44·4 mL (35·4; –25·2 to 114·0; p=0·21) at week 16 (figure 1A). The percentage of predicted FVC differences at week 8 (least squares mean 1·8%; SE 0·7; 95% CI 0·4 to 3·2; p=0·014) and week 16 (1·8%; 0·8; 0·2 to 3·4; p=0·028) were statistically significant, indicating potential benefit of inhaled treprostinil compared with placebo (figure 1B). A subgroup analysis of patients with idiopathic interstitial pneumonia showed significant FVC differences at week 16 (108·2 mL; SE 46·9; 95% CI 15·3 to 201·1; p=0·023) although not at week 8 (46·5 mL; 39·9; –32·5 to 125·5; p=0·25; figure 2A), and significant differences in percentage of predicted FVC at week 8 (2·0%; SE 0·9; 95% CI 0·1 to 3·8; p=0·037) and week 16 (2·9%; 1·1; 0·7 to 5·0; p=0·0096) favouring inhaled treprostinil (figure 2B). Further analysis of patients with idiopathic pulmonary fibrosis showed non-significant FVC differences of 84·5 mL (SE 52·7; 95% CI –20·4 to 189·5;

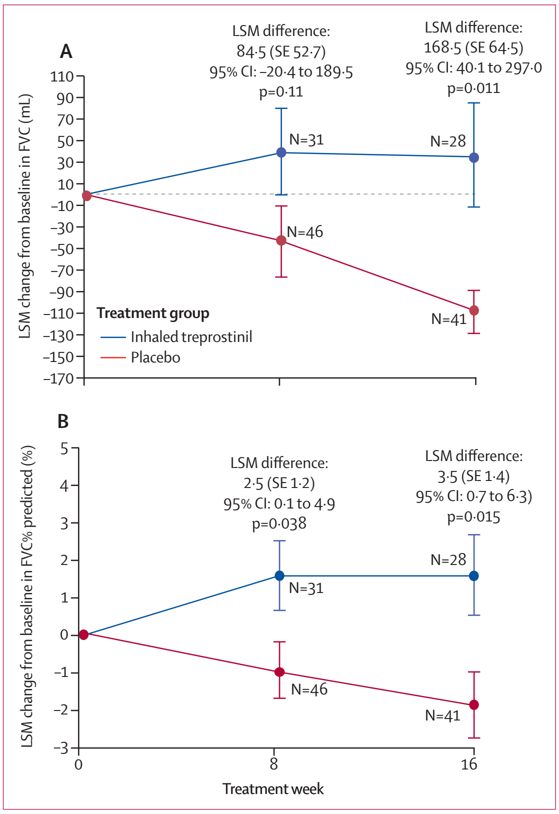

Figure 3: **Change in FVC at week 8 and week 16 for patients with idiopathic pulmonary fibrosis**
(A) LSM change in FVC (mL) by week for the subgroup of patients with idiopathic pulmonary fibrosis who received treprostinil or placebo. (B) LSM change in percentage of predicted FVC by week for the subgroup of patients with idiopathic pulmonary fibrosis. Bars above and below the dots represent the SE. Mixed model repeated measures methodology was used to compare differences between the inhaled treprostinil and placebo groups. FVC=forced vital capacity. LSM=least squares mean.

See Online for appendix

	Inhaled treprostinil (n)	Placebo (n)	Placebo-corrected difference in week-16 FVC, mL	p value
FVC% predicted				
<60	62	50	27·5 (53·3; –77·4 to 132·4)	0·61
≥60	67	74	59·2 (47·8; –34·9 to 153·4)	0·22
DLCO% predicted				
<27	52	61	35·4 (51·6; –66·2 to 137·1)	0·49
≥27	70	60	33·3 (48·5; –62·3 to 128·9)	0·49
Pulmonary vascular resistance, Wood units				
<5·275	64	75	–1·6 (47·9; –95·9 to 92·8)	0·97
≥5·275	65	49	112·5 (52·6; 9·0 to 215·9)	0·033
Mean pulmonary arterial pressure, mm Hg				
<35	63	63	63·4 (50·2; –35·4 to 162·1)	0·21
≥35	66	61	25·6 (50·2; –73·2 to 124·4)	0·61
NT-proBNP, pg/mL				
<503·85	62	75	19·9 (53·7; –86·3 to 126·1)	0·71
≥503·85	63	47	94·4 (47·4; 0·7 to 188·2)	0·048
6-min walk distance, m				
<259	63	56	64·5 (51·7; –37·3 to 166·4)	0·21
≥259	66	68	27·6 (48·7; –68·4 to 123·5)	0·57

Data are mean (SE; 95% CI) unless otherwise indicated. DLCO=diffusing capacity for carbon monoxide. FVC=forced vital capacity. NT-proBNP=N-terminal pro-brain natriuretic peptide.

Table 2: **Placebo-corrected difference in week-16 FVC stratified by median baseline clinical characteristics**

p=0·11) at week 8 and significant differences of 168·5 mL (64·5; 40·1 to 297·0; p=0·011) at week 16 (figure 3A), and differences in percentage of predicted FVC at week 8 and week 16 of 2·5% (SE 1·2; 95% CI 0·1 to 4·9; p=0·038) and 3·5% (1·4; 0·7 to 6·3; p=0·015), respectively, compared with placebo (figure 3B). Of note, 49 (53%) of 92 patients with idiopathic pulmonary fibrosis were on antifibrotic therapy at baseline. FVC changes for patients with connective tissue disease-associated ILD and combined pulmonary fibrosis and emphysema are shown in the appendix (pp 4–5). Histograms showing FVC categorical changes in 5% increments for the overall study population and the four disease categories are provided in the appendix (pp 6–8).

We stratified change in FVC over 16 weeks by baseline lung function (median percentage of predicted FVC and median percentage of predicted DLCO), haemodynamics (median pulmonary vascular resistance and mean pulmonary arterial pressure), median baseline NT-proBNP concentration, and median baseline 6-min walk distance (table 2). We identified no responder or non-responder subgroup based on analyses of percentage of predicted FVC (<60% or ≥60%), percentage of predicted DLCO (<27% or ≥27%), or mean pulmonary arterial pressure (<35 mm Hg or ≥35 mm Hg). However, a subgroup analysis of 114 patients with pulmonary vascular resistance of 5·275 Wood units or greater showed a significant difference favouring inhaled treprostinil versus placebo, with a mean placebo-corrected difference in FVC of 112·5 mL at 16 weeks (SE 52·6; 95% CI 9·0 to 215·9; p=0·033; table 2). Similarly, a subgroup analysis of 110 patients with NT-proBNP concentration of 503·85 pg/mL or greater showed a significant difference favouring inhaled treprostinil compared with placebo, with a placebo-corrected difference in FVC of 94·4 mL at 16 weeks (SE 47·4; 95% CI 0·7 to 188·2; p=0·048; table 2).

14 patients in the inhaled treprostinil group were on pirfenidone versus 18 patients in the placebo group. There was no significant placebo-corrected difference favouring inhaled treprostinil at 16 weeks (91·5 mL; SE 110·2; 95% CI –134·2 to 317·1; p=0·41) in the pirfenidone-treated subgroup. Seven patients in the inhaled treprostinil group were on nintedanib versus 15 patients in the placebo group. The placebo-corrected difference for inhaled treprostinil was 113·0 mL at 16 weeks (SE 77·1; 95% CI –46·9 to 272·8; p=0·16) in the nintedanib-treated subgroup. When patients on pirfenidone or nintedanib were evaluated as a group, those receiving inhaled treprostinil had no statistically significant difference in placebo-corrected FVC (81·5 mL; SE 71·0; 95% CI –60·9 to 223·8; p=0·26) or percentage of predicted FVC (1·2%; 1·5; –1·8 to 4·2; p=0·43) at week 16.

The most frequent adverse events, which have been reported previously, included cough, headache, dyspnoea, dizziness, nausea, fatigue, and diarrhoea.[12] We found no difference in the frequency of these adverse events according to disease subtype (table 3). We also observed no difference in exacerbations between disease subtypes (appendix p 3).

Regarding safety, no significant treatment-related changes associated with inhaled treprostinil in pulse oximetry or supplemental oxygen use were reported during the study. However, there were significantly fewer lung disease exacerbations in the treprostinil group than the placebo group. Specifically, 43 (26%) of 163 patients in the treatment group had an exacerbation of underlying lung disease compared with 63 (39%) of 163 patients in the placebo group (p=0·02 by Fisher's exact test).[12] Time to investigator-reported exacerbations in the two groups is shown in the appendix (p 8), with inhaled treprostinil associated with a significant treatment effect (log-rank p=0·040).

Discussion

The INCREASE study was designed to evaluate the effects of inhaled treprostinil in patients with various

ILDs and associated pulmonary hypertension. The study met its primary endpoint: compared with placebo, treprostinil improved exercise capacity, assessed by 6-min walk distance, from baseline at 16 weeks.[12] The study also met several secondary endpoints, including time to clinical worsening and change in concentration of NT-proBNP, a marker of cardiac dysfunction that likely reflects right ventricular strain in patients with pulmonary hypertension due to interstitial lung disease. Lung function, specifically spirometry, was measured at baseline and at week 8 and week 16 as a safety measure to ensure that there were no deleterious effects of inhaled treprostinil. We felt that investigation of any deleterious effects was important because of the patients' pre-existing lung disease. A noteworthy finding previously reported in the primary publication[12] was that, rather than causing any decrement, inhaled treprostinil was unexpectedly associated with a placebo-corrected improvement in FVC. Further subgroup analyses revealed the FVC difference between the inhaled treprostinil group and placebo group to be larger in the idiopathic interstitial pneumonia subgroup, and even more so in the idiopathic pulmonary fibrosis subpopulation.

FVC is widely accepted as the standard efficacy endpoint for clinical trials in idiopathic pulmonary fibrosis and other fibrotic lung disorders.[13] Indeed, clinical trials evaluating change in FVC over 52 weeks have resulted in the approval of both pirfenidone and nintedanib for the treatment of idiopathic pulmonary fibrosis.[3,4] Nintedanib has since been approved for other fibrotic disorders, including scleroderma-associated ILD and a broader group of ILDs characterised by a progressive fibrotic phenotype.[5,6] The disease groups included in a previous cohort study[6] of nintedanib were very similar to those of the INCREASE study.[12] Our findings lend support to the study of different forms of fibrotic disease as a group, although the idiopathic pulmonary fibrosis subgroup did show the strongest efficacy signal.

No drug has been shown to have an effect on fibrosis when administered via inhalation. However, there is inherent attractiveness to this mode of delivery because of greater deposition of drug at the site of disease, resulting in fewer systemic side-effects and preservation, or possibly improvement, of ventilation–perfusion matching. Fibrotic lung diseases, and idiopathic pulmonary fibrosis in particular, are characterised by areas of vascular ablation and perivascular fibrosis, which raises the issue of adequate systemic drug delivery to high-value target cells, including fibroblasts and myofibroblasts.[14] The finding of a placebo-corrected improvement in FVC indicates that inhaled treprostinil might have distinct antifibrotic properties. Indeed, animal studies and biological pathways support this concept.[10,11] Amelioration of loss of lung function has been described previously with sildenadil, another medication approved in the USA and Europe for the treatment of pulmonary arterial hypertension, in patients with idiopathic pulmonary fibrosis on background nintedanib.[15] This observation lends credence to the possibility that the pulmonary vasculature itself might be involved in the perpetuation of the fibrotic process or that pulmonary hypertension and fibrosis have shared pathways. However, this synergy was not replicated when sildenafil was combined with pirfenidone.[16]

	Idiopathic interstitial pneumonia including idiopathic pulmonary fibrosis (n=146)	Idiopathic pulmonary fibrosis only (n=92)	Combined pulmonary fibrosis and emphysema (n=82)	Connective tissue disease-associated ILD (n=72)
Number of subjects with adverse event of interest	115 (79%)	71 (77%)	63 (77%)	49 (68%)
Cough	55 (38%)	30 (33%)	32 (39%)	31 (43%)
Dyspnoea	44 (30%)	24 (26%)	28 (34%)	17 (24%)
Headache	35 (24%)	19 (21%)	22 (27%)	15 (21%)
Dizziness	29 (20%)	17 (18%)	15 (18%)	5 (7%)
Nausea	28 (19%)	18 (20%)	11 (13%)	9 (13%)
Fatigue	20 (14%)	12 (13%)	13 (16%)	11 (15%)
Diarrhoea	23 (16%)	13 (14%)	9 (11%)	6 (8%)
Productive cough	4 (3%)	3 (3%)	2 (2%)	5 (7%)
Dyspnoea on exertion	4 (3%)	2 (2%)	2 (2%)	1 (1%)
Upper-airway cough syndrome	3 (2%)	1 (1%)	1 (1%)	2 (3%)
Sinus headache	2 (1%)	1 (1%)	1 (1%)	0
Muscle fatigue	1 (1%)	1 (1%)	1 (1%)	0

Data are n (%). ILD=interstitial lung disease.

Table 3: **Adverse events by disease cause**

Two of our subgroup analyses showed a significant difference in FVC change between the inhaled treprostinil group and the placebo group. These analyses were in patients with higher pulmonary vascular resistance and higher NT-proBNP concentration. Therefore, pulmonary vessels themselves might contribute to the restrictive physiology, perhaps through vascular compliance, which is ameliorated by inhaled treprostinil. An alternative, speculative concept is that the presence of more severe pulmonary hypertension might hasten the progression of fibrosis. A further hypothesis is that these FVC findings are related to improved right ventricular function or cardiac output in those receiving inhaled treprostinil, as evidenced by the greater treatment effect in those with higher baseline pulmonary vascular resistance and NT-proBNP concentration, but less striking differences when stratifying by baseline mean pulmonary arterial pressure. Decreased right ventricular size and function and improved cardiac output in those with more severe pulmonary hypertension could lead to improvement in respiratory muscle function and thus FVC.

It is interesting to compare the findings in our idiopathic pulmonary fibrosis population with those of the pivotal phase 3 studies of pirfenidone and

nintedanib.[2–4,17,18] First, INCREASE was only a 16-week study compared with 52-week and 72-week studies for these other agents. Whether our results will dissipate, be sustained, or improve up to 52 weeks is open to speculation given how unpredictable disease behaviour can be over time. The magnitude of the difference was very similar with inhaled treprostinil at 16 weeks (168·5 mL) compared with the combined pirfenidone (148 mL per year) and nintedanib (110·9 ml per year) datasets at 52 weeks.[17,18] However, in addition to the different follow-up periods, there were varying imputation methods and nuanced differences that limit meaningful comparisons between studies.[18,19] The difference in the FVC change in INCREASE was partly driven by a numerical FVC increase in the treatment group, which contrasts with the pirfenidone and nintedanib studies, where the difference lay in the rate of decrement in both groups (although there were some patients with numerical increases in FVC).[18,19] This fact raises the question of whether inhaled treprostinil can ameliorate fibrosis; this is conceivable perhaps for areas of fresh collagen deposition or through so-called switching off of myofibroblasts that might contribute to restrictive physiology through their contractile properties.[20–22] An alternative explanation is that treprostinil improved vessel capacitance and stiffness, affecting the measured FVC.

Although we observed a significant difference in the change in percentage of predicted FVC over the 16-week study period for the cohort as a whole, the difference was not significant when evaluated FVC by change in mL. This apparent discrepancy could be due to the narrower CIs when FVC is expressed as a percentage of the predicted value. Many patients with idiopathic pulmonary fibrosis were already on antifibrotic therapy; however, the number of patients on nintedanib or pirfenidone in combination with inhaled treprostinil was too small to draw efficacy conclusions. The smaller numerical difference when combining the two antifibrotics (81·5 mL) versus each individually (113·0 mL for patients on nintedanib and 91·5 mL for patients on pirfenidone) is a function of MMRM statistical methodology. Nonetheless, the numerical differences show the potential role of combination therapy for idiopathic pulmonary fibrosis and targeting the disease concomitantly via the systemic and inhaled routes.

FVC was measured as a safety endpoint in the context of the INCREASE study. Other pulmonary function tests, including DLCO, were also measured as safety endpoints but did not show a difference between groups. A longer-term study of inhaled treprostinil in patients with ILD and pulmonary hypertension is ongoing and will provide information on gas exchange (NCT02633293). Other safety endpoints, including pulse oximetry and change in supplemental oxygen needs, did not show any deleterious effects, mitigating concerns about potential worsening of ventilation–perfusion matching. Additionally, the incidence of investigator-reported acute exacerbations was significantly less in the treprostinil group, allaying any concerns that this inhaled medication might induce acute exacerbations. Therefore, it is possible that inhaled treprostinil might actually ameliorate acute exacerbations of the underlying ILD.

Our analysis has its limitations. First, this was a post-hoc analysis of a parameter that was initially intended as a safety endpoint, and the study was not powered to detect differences in FVC among the different subgroups in the analysis. The study was of relatively short duration, with 21% of patients discontinuing prematurely before week 16.[12] The number of patients was relatively small for the subgroup analyses. There was no efficacy signal from the connective tissue disease-associated ILD group or the combined pulmonary fibrosis and emphysema group, which raises questions about global antifibrotic properties and whether our findings are relevant for only certain subgroups of fibrotic disorders. Also, the relatively rapid rate of FVC decrement in the placebo group over a short period of time was unexpected. Aside from patients with more severe disease being at higher risk of progression, an interesting hypothesis is that perhaps the pulmonary vasculature is mechanistically linked to the progression of fibrosis.[23] Finally, the finding of fewer acute exacerbations in the inhaled treprostinil group should be regarded with caution, since these acute exacerbations were investigator-determined and not centrally adjudicated. The unusually high rate of acute exacerbations in both study groups is noteworthy. It is possible that patients with more advanced disease who have any worsening are more likely to be increasingly symptomatic, with the default labelling of an acute exacerbation, without necessarily fulfilling all the criteria. We cannot rule out the possibility that any inhaled therapy, be it placebo or treatment, might increase the propensity for acute exacerbations.

In conclusion, inhaled treprostinil appears to have a salutary effect on loss of lung function in patients with ILD and associated pulmonary hypertension. This finding, although intriguing and hypothesis generating, warrants further validation in a prospective, randomised, placebo-controlled study. A clinical trial of inhaled treprostinil is underway in patients with idiopathic pulmonary fibrosis, with or without associated pulmonary hypertension (NCT04708782). This study will use a primary endpoint of change in FVC over 52 weeks and will support the findings of our post-hoc analysis.

Contributors

SDN, AW, PS, ES, LDE, AN, and VFT made substantial contributions to the conception and design of the work. SDN, AW, SR, AC, SJ, HD, DJDLZ, SS, CK, LM-G, and VFT contributed to the acquisition of the study data. Data were analysed by SDN, AW, PS, ES, LDE, AN, and VFT. LDE was responsible for the statistical analysis. SDN, AW, and VFT participated on the INCREASE steering committee during the study. SDN, AW, SR, AC, SJ, HD, DJDLZ, SS, CK, LM-G, PS, ES, AN, and VFT contributed to data interpretation, and to drafting and revision of the manuscript. SDN, ES, and LDE have accessed and verified the data. All authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and

approved the manuscript. The corresponding author and all co-authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SDN has received research funding and consulting fees from United Therapeutics, and consulting fees from Boehringer Ingelheim, Roche-Genentech, and Galapagos; he is on the speaker's bureau for Boehringer Ingelheim and Roche-Genentech. AW reports grants from United Therapeutics, during the conduct of the study. SR reports grants from United Therapeutics, during the conduct of the study; grants and personal fees from United Therapeutics and Janssen Pharmaceuticals; and personal fees from Altavant Sciences, Liquidia Technologies, Insmed, and Bayer Pharmaceuticals, outside the submitted work. AC reports grants from United Therapeutics, during the conduct of the study. SJ reports grants from United Therapeutics, during the conduct of the study; grants and personal fees from Bayer Pharmaceuticals and Janssen Research & Development; and grants from Bellerophon Therapeutics, outside the submitted work. HD reports grants from United Therapeutics, during the conduct of the study; and grants and personal fees from Actelion Pharmaceuticals, outside the submitted work. DJDLZ reports grants from United Therapeutics, during the conduct of the study. SS reports grants from United Therapeutics, during the conduct of the study; personal fees and non-financial support from Bayer Pharmaceuticals, United Therapeutics, and Actelion Pharmaceuticals; personal fees from Liquidia, Altavant Sciences, GSK, and Boehringer Ingelheim; and grants from ACCP CHEST ILD, outside the submitted work. CK reports grants from United Therapeutics, during the conduct of the study; and personal fees from United Therapeutics, Actelion, Boehringer Ingelheim, and Genentech, outside the submitted work. LM-G reports grants and personal fees from United Therapeutics, during the conduct of the study; and personal fees from United Therapeutics, Janssen Pharmaceuticals, and Bayer Pharmaceuticals, outside the submitted work. PS, ES, LDE, and AN report personal fees from United Therapeutics, during the conduct of the study; and personal fees from United Therapeutics, outside the submitted work. VFT reports grants from United Therapeutics, during the conduct of the study; and personal fees from United Therapeutics, outside the submitted work.

Data sharing

Qualified researchers who provide methodologically sound, genuine research proposals can submit data requests to United Therapeutics Corporation to obtain specific de-identified clinical trial data.

To **submit data requests** see www.utcrequests.com

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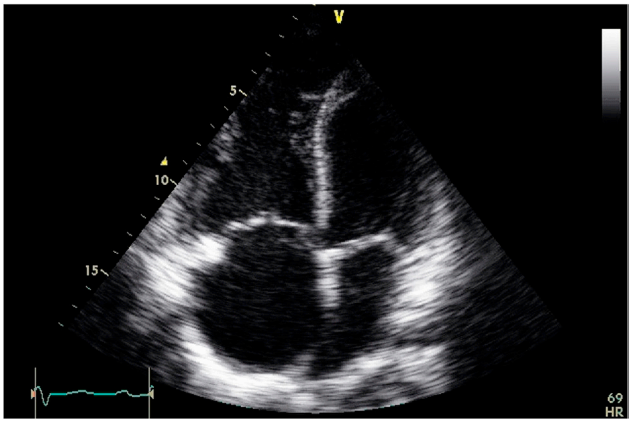
EXHIBITS 21 - 39

EXHIBIT 21



Conclusion: Our study failed to show correlation of global RVLS to established echocardiographic parameters of RV dysfunction in a cohort of patients with severe PH. However, RVGS is a developing quantitative, non-invasive parameter that requires more study to define the relationship of RVGS to mortality and morbidity in PH.

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A Comparative Study of Right Ventricular Strain to Established Echocardiographic Parameters in Pulmonary Hypertension

D. Seaton,[1] A. Yamada,[2] J. Chan,[3] B. Shearer,[1] K. Aldridge,[1] F. Kermeen.[4] [1]Queensland Nuclear Imaging, The Prince Charles Hospital, Brisbane, Australia; [2]Heart Foundation Research Centre, Griffith University, Gold Coast, Australia; [3]Cardiology Department, The Prince Charles Hospital, Brisbane, Australia; [4]Queensland Lung Transplant Unit, The Prince Charles Hospital, Brisbane, Australia.

Purpose: Right ventricular (RV) function is a strong predictor of morbidity and mortality in pulmonary hypertension (PH). The measurement of right ventricular global strain (RVGS) is a developing quantitative, non-invasive parameter in the assessment of the RV. The aim of this study was to compare global RV longitudinal strain (RVLS) relative to established echocardiographic indices in the assessment RV dysfunction in a cohort of PH patients with pseudo-normalised tricuspid annular plane systolic excursion (TAPSE) and S' velocity.
Methods: 52 consecutive patients (mean age 56±2.2, mean NYHA-FC 3.2, 25 IPAH, 13 PAH-CVD, 3 PAH-CHD, 5 CTEPH, 5 out of proportion PHT & 1 Porto-pulmonary-PH) underwent 2D transthoracic speckle tracking echocardiography with modified apical 4 chamber view focused on RV. Global RVLS was measured offline using EchoPAC BT011 GE software. Global RVLS was compared to established RV echocardiographic parameters using Pearson's correlation.
Results: Global RVLS demonstrated modest correlation with RV dysfunction by visual estimation (r=0.458, p=0.001; r=0.512,p=0.001) and NYHA functional class (r=0.487,p<0.001; r=.0481,p<0.001) compared with other parameters of RV function, including TAPSE (r=0.017; p=0.916), RV S' tissue Doppler (r=-0.273; p=0.069), PAEDP (r=0.063; p=0.71) and fractional area change (r=-0.337; p = 0.025).

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Inhaled Treprostinil in Group-3 Pulmonary Hypertension

M. Agarwal,[1] A.B. Waxman.[2] [1]Pulmonary Critical Care and Cardiovascular Medicine, Brigham & Women's Hospital, Boston, MA; [2]Center for Pulmonary Heart Disease, Brigham & Women's Hosp, Boston, MA.

Purpose: WHO Group-3PH is frequently encountered and adversely affects patients' quality of life and survival. Treatment with systemic pulmonary vasodilators may result in V/Q imbalance. Inhaled prostanoid therapy is delivered directly to well ventilated lung units preserving V/Q, and reducing undesirable alterations in perfusion. We conducted a retrospective assessment of Group-3 PH patients (pts) receiving inhaled Treprostinil (iTre) to investigate the effects of iTre on dyspnea, 6MWD, BDI, and WHO FC.
Methods: We followed 35 WHO Group-3PH pts treated with iTre for 6 months (mo). 15 had obstructive, 15 restrictive disease and 5 were classified as mixed obstructive/restrictive. All pts had a diagnostic right heart cath prior to treatment. Baseline (BL) hemodynamics: mPAP 44.37 +/- 9.80, PAOP 9.68 +/- 4.71. In one patient CO and PVR was not reported. For the remaining 34 pts CO 4.7 +/- 1.34, and PVR 8.775WU +/- 4.7625. All pts started on 3-breaths (br) 4x daily and increased to goal of 9-12 br 4x daily as tolerated. 6-MWD, BDI, WHO FC, AE's, number of breaths and subjective improvement were assessed.
Results: All 35 pts started iTre, 16 women, 19 men, mean age of 68.77 +/- 9.77. There were no significant changes in WHO FC (p= 0.08), 30 pts had subjective improvement. The most common AE was cough. Of the 35 pts, 9 were on therapy less than 6 mo; 1 death unrelated to therapy, 2 stopped because of intolerance, 3 stopped for lack of efficacy, 2 lost to follow up, and 1 who entered hospice. 26 pts remained on therapy for at least 6 mo. Number of breaths at 6 months was 6 (n=2), 9 (n=15), 12 (n=3), and 15 (n=1). 24 of these pts reported subjective improvement and 21 had 6MWD available at BL and 6mos. Mean change in 6 MWD +60.85m +/- 92.60 (median change +45m, p = 0.0019). In patients with obstruction 6MWD improved by a mean of 71m +/- 120 (median +26m), and restriction by 50m +/- 57 (median +61m). There was no significant change in the Borg Dyspnea Index (p=0.8783).
Conclusion: Group-3 PH can be effectively and safely treated with iTre. Inhaled Treprostinil may offer a well-tolerated treatment in advanced lung disease patients complicated by pulmonary vascular remodeling. A prospective clinical trial is indicated.

EXHIBIT 22

ORIGINAL ARTICLE

Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis

Rajeev Saggar,[1] Dinesh Khanna,[2] Anjali Vaidya,[3] Ariss Derhovanessian,[4] Paul Maranian,[2] Erin Duffy,[5] John A Belperio,[4] Sam S Weigt,[4] Shiv Dua,[6] Shelley S Shapiro,[4] Jonathan G Goldin,[7] Fereidoun Abtin,[7] Joseph P LynchIII,[4] David J Ross,[4] Paul R Forfia,[8] Rajan Saggar[4]

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For numbered affiliations see end of article.

Correspondence to
Dr Rajan Saggar, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Ave. CHS 37-131, Los Angeles, CA 90095, USA; rsaggar@mednet.ucla.edu

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ABSTRACT

Background Pulmonary hypertension (PH)-targeted therapy in the setting of pulmonary fibrosis (PF) is controversial; the main clinical concern is worsening of systemic hypoxaemia. We sought to determine the effects of gentle initiation and chronic administration of parenteral treprostinil on right heart function in patients with PF associated with an advanced PH phenotype.

Methods Open-label, prospective analysis of patients with PF-PH referred for lung transplantation (LT). Advanced PH was defined as mean pulmonary artery pressure (mPAP) ≥35 mm Hg. We compared haemodynamics, Doppler echocardiography (DE), oxygenation, dyspnoea and quality of life indices, and 6 min walk distance (6MWD) before and 12 weeks after parenteral treprostinil.

Results 15 patients were recruited in the study. After therapy, there were significant improvements in right heart haemodynamics (right atrial pressure (9.5 ± 3.4 vs 6.0 ± 3.7); mPAP (47 ± 8 vs 38.9 ± 13.4); CI (2.3 ± 0.5 vs 2.7 ± 0.6); pulmonary vascular resistance (698 ± 278 vs 496 ± 229); transpulmonary gradient (34.7 ± 8.7 vs 28.5 ± 10.3); mvO_2 (65 ± 7.2 vs 70.9 ± 7.4); and stroke volume index (29.2 ± 6.7 vs 33 ± 7.3)) and DE parameters reflecting right heart function (right ventricular (RV) end diastolic area (36.4 ± 5.2 vs 30.9 ± 8.2 cm^2), left ventricular eccentricity index (1.7 ± 0.6 vs 1.3 ± 0.5), tricuspid annular planar systolic excursion (1.6 ± 0.5 vs 1.9 ± 0.2 cm)). These changes occurred without significant alteration in systemic oxygenation, heart rate, or mean systemic arterial pressure. In addition, improvements were seen in 6MWD (171 ± 93 vs 230 ± 114), 36-Item Short Form Health Survey Mental Component Summary aggregate (38 ± 11 vs 44.2 ± 10.7), University of California, San Diego Shortness of Breath Questionnaire (87 ± 17.1 vs 73.1 ± 21), and brain natriuretic peptide (558 ± 859 vs 228 ± 340).

Conclusions PH-targeted therapy may improve right heart haemodynamics and echocardiographic function without affecting systemic oxygen saturation in an advanced PH phenotype associated with RV dysfunction in the setting of PF.

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Key messages

What is the key question?

- What are the effects of parenteral treprostinil on right heart function of patients with pulmonary fibrosis (PF) referred for lung transplantation (LT) with an advanced pulmonary hypertension (PH) phenotype?

What is the bottom line?

- Parenteral treprostinil improves right heart haemodynamics and echocardiographic function without affecting systemic oxygen saturation in PH-PF with an advanced PH phenotype.

Why read on?

- This pilot study suggests parenteral treprostinil improves right ventricle function and is a safe therapeutic option in patients with PH-PF with an advanced PH phenotype; as such, this approach may be a consideration for patients with advanced PH-PF if they are ineligible for, or as a bridge to, LT.

INTRODUCTION

Pulmonary hypertension (PH) may complicate pulmonary fibrosis (PF) of different causes, but few studies have focused on the treatment of advanced PH in this context.[1–4] Furthermore, no prospective chronic parenteral prostanoid administration studies are available in patients with PF homogenised for the less common advanced PH phenotype, characterised by significantly altered right heart haemodynamics and right ventricular (RV) dysfunction. We previously reported a case where the rationale for parenteral treprostinil as a bridge to lung transplantation (LT) was outlined in the index patient with PF-PH for this study.[5] Importantly, parenteral prostanoid therapy associated with worsening of ventilation-perfusion (V-Q) mismatch and subsequent hypoxaemia remains a major clinical concern. The purpose of this pilot study was to evaluate the effects of acute and subsequent chronic parenteral treprostinil therapy on right heart haemodynamics and echocardiographic function in patients with PH referred for LT in the setting of an advanced PH phenotype and right heart dysfunction.

MATERIALS AND METHODS

This study was approved by the IRB at University of California, Los Angeles (UCLA IRB# 07-11-087-03; clinicaltrials.gov Identifier NCT00705133). We recruited 15 outpatients with PF referred to our LT programme between July 2008 and January 2011 who had advanced PH based on right heart catheterisation (RHC) (figure 1). Sarcoidosis and systemic sclerosis spectrum of disease were excluded, as were patients requiring >10 L/min of oxygen at baseline. Importantly, threshold measures of right heart size and/or function were not required for study enrolment. Patients with combined pulmonary fibrosis emphysema were included.[6] Formal pulmonary rehabilitation was not prescribed during the study period.

Advanced PH was defined using haemodynamic criteria: mean pulmonary artery pressure (mPAP) ≥ 35 mm Hg, pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) > 240 dyn s/cm^5. Other PH aetiologies were ruled out based on current recommendations.[7] All follow-up RHCs were performed after ≥12 weeks of stable dose background PH-targeted therapy, and background PF-related therapy remained unaltered during the study period.

Six minute walk distance and oxygen supplementation protocols

Patients were ambulated per American Thoracic Society criteria with a modification regarding oxygen supplementation (OS), given the inherent hypoxaemia in this patient population (see online supplementary repository).[8]

Pulmonary function testing and Doppler echocardiogram protocols

Pulmonary function testing (PFT) was obtained at treprostinil initiation and at 12 weeks and included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio and single-breath diffusing capacity for carbon monoxide (DLCO). Total lung capacity (TLC) was only performed at baseline. Doppler echocardiogram (DE) was performed using conventional equipment (Hewlett-Packard, Palo Alto, California, USA) at baseline and 12 weeks (see online supplementary repository).

Dyspnoea and quality of life assessments

Dyspnoea was measured with the University of California, San Diego Shortness of Breath (UCSD SOB) questionnaire and the Borg Dyspnoea Index (BDI) (see online supplementary repository).

Health-related quality of life was measured with the 36-Item Short Form Health Survey (SF-36). SF-36 scales are summarised into Physical Component (PCS) and Mental Component (MCS) Summary scores. The eight SF-36 scales and the PCS and MCS scores are standardised to a mean of 50 and an SD of 10 in the general US population. Minimally important difference (MID) estimates for SF-36 PCS and MCS are 2.5 points (see online supplementary repository).

Parenteral treprostinil titration protocol

All patients were hospitalised for 48 h for treprostinil initiation and uptitration (see online supplementary repository).

High-resolution CT lung parenchymal scoring

Thin slice (<3 mm) CT scans were used for objective assessment of lung parenchymal abnormality at baseline (see online supplementary repository).

Study parameters

Patient assessments were made at baseline and after 12 weeks of parenteral treprostinil and included RHC and systemic haemodynamics, echocardiographic parameters, 6 min walk distance (6MWD), PFT, systemic and central oxygenation, brain natriuretic peptide (BNP), and SF-36/UCSD SOB questionnaires.

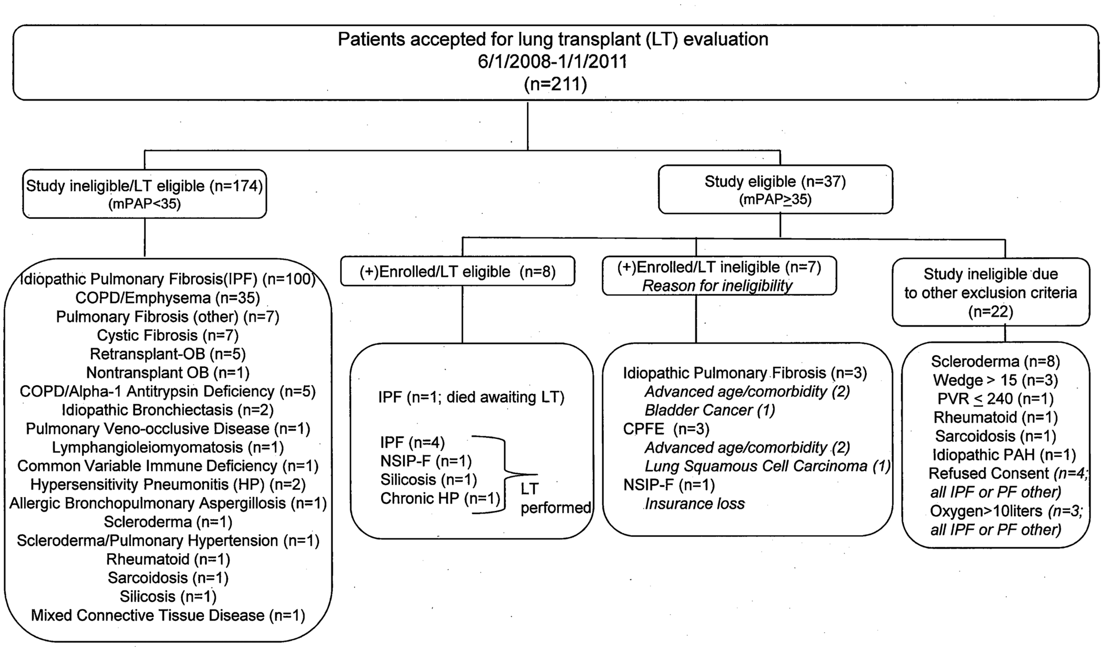

Figure 1 Recruitment of patients (n=15) with pulmonary fibrosis and advanced pulmonary hypertension being evaluated for lung transplantation at a single tertiary medical centre between July 2008 and January 2011. CPFE, combined pulmonary fibrosis emphysema; mPAP, mean pulmonary artery pressure; NSIP-F, non-specific interstitial pneumonia fibrosis; PAH, pulmonary arterial hypertension; PF, pulmonary fibrosis; PVR, pulmonary vascular resistance.

Statistics

Baseline characteristics were described as frequencies (%) for categorical variables and means (SD) for continuous variables. Clinical, haemodynamic, and echocardiographic data were reported at baseline and 12 weeks, and the Shapiro–Wilk test was used to assess the normaility of the distributions of baseline and week 12 data. For variables where normality was rejected at the $p<0.05$ level, median (IQR) values were reported and the Wilcoxon signed rank test was used to compare DLCO (% predicted), FVC%/DLCO%, 6 min walk 10 L face mask (FM) (% saturation), SF-36 Physical Functioning, stroke volume (SV), and systolic blood pressure (SBP) measures at baseline and week 12. For all other clinical, haemodynamic, and echocardiographic variables, mean (SD) were reported and paired t tests were used to compare variables at baseline and week 12. Q-values were computed to assess the impact of multiple comparisons in the domains of pulmonary function, quality of life, and haemodynamics. Analyses were conducted with Stata V.13 (Stata Corp LP, College Station, Texas, USA), and p values <0.05 were considered statistically significant.

RESULTS

Demographics

Fifteen patients aged 63 ± 15 years (mean ± SD) (20% female) referred for LT met all study criteria and agreed to enrolment (figure 1). Baseline WHO functional class was equally split with 53% class III (n=8) and 47% class IV (n=7). Background PH therapy (≥12 weeks of stable dose therapy) and the underlying clinical diagnoses regarding the aetiology of the PF are displayed in table 1. A subgroup of clinical diagnoses (n=10) had pathological confirmation made by surgical lung biopsy (n=2), eventual explantation (n=7), or autopsy (n=1) (see online supplementary repository table S2). Individual patient data are presented in the repository (see online supplementary table S1). The extent of baseline lung parenchymal abnormality by high-resolution CT (HRCT) chest imaging is reported for each patient in the repository (see online supplementary table S2).

Safety/adverse events

Of the 15 patients, 14 patients received subcutaneous treprostinil and 1 patient was placed on intravenous treprostinil.[5] The treprostinil dose for the group at 12 weeks was 34 ± 21 ng/kg/min (mean ± SD) and a range of 18–97 ng/kg/min. During inpatient treprostinil initiation, there were no changes in vital signs, particularly oxygen saturation by peripheral pulse oximetry (PPO), or adverse haemodynamic changes that led to acute discontinuation of the medication. During inpatient and outpatient treprostinil uptitration, patients experienced typical prostanoid effects, including jaw pain, diarrhoea, lower extremity bone pain, site pain/reaction, headache, and/or flushing.[9]

Pulmonary function testing, 6MWD, and oxygen status

The mean (±SD) baseline % predicted values for FEV_1, FVC, TLC, and FEV_1/FVC ratio were 62 (17), 62 (21), 70 (15), 77 (11), and 24 (13), respectively and the median (IQR) baseline % predicted value for DLCO was 24 (13); for the cohort of patients without CPFE (n=12), baseline TLC was 67 (16). There were no significant changes in PFT parameters following 12 weeks of treprostinil (table 2). Comprehensive individual patient data are presented in the repository (see online supplementary table S3).

The baseline 6MWD (mean ± SD) was 171 ± 93 m with a resting room air pulse oximetry of 83 ± 7%. All except one

Table 1 Patient demographics, underlying fibrotic lung disease clinical subtype, and background PH-targeted therapy

Patient characteristics	N=15 Mean	SD
Age in years	63	15
	N	Per cent
NYHA class		
III	8	53
IV	7	47
Race		
Hispanic	8	53
Caucasian	4	27
Filipino/Japanese	2	13
Middle Eastern	1	7
Fibrotic lung disease clinical subtype		
Idiopathic pulmonary fibrosis	8	53
NSIP-fibrosis	2	13
PF/emphysema (CPFE)	3	20
Chronic Hypersensitivity Pneumonitis (HP)	1	7
Silicosis	1	7
Background therapy		
Sildenafil monotherapy	4	27
Bosentan monotherapy	2	13
Sildenafil/bosentan combination	3	20
None	6	40

CPFE, combined pulmonary fibrosis/emphysema; NSIP, non-specific interstitial pneumonia; NYHA, New York Heart Association; PF, pulmonary fibrosis; PH, pulmonary hypertension.

Table 2 Pulmonary function testing, oxygen requirements, and 6 min walk distance with Borg Dyspnoea Index (BDI) scores at baseline and end of study

	Baseline N=15 Mean (SD)	12 weeks N=15 Mean (SD)	p Value*
Pulmonary function			
FVC, % predicted	62 (21)	63 (18)	0.687
FEV_1, % predicted	62 (17)	64 (16)	0.215
FEV_1/FVC	77 (11)	80 (12)	0.134
TLC, % predicted			
All patients	70 (15)	–	
Patients without CPFE, n=12	67 (16)	–	
DLCO, % predicted†	24 (13)	22 (11)	0.206†
FVC%/DLCO%†	2.5 (2.4)	3.0 (1.6)	0.625†
Oxygen flow (L/min)	3.9 (1.9)	3.9 (2.1)	>0.999
6 min walk:			
6 min walk distance (m)	171 (93)	230 (114)	<0.001
Room air % saturation	83 (7)	80 (10)	0.078
10 L face mask, % saturation†	98 (3)	99 (4)	0.372†
10 L face mask, % saturation nadir	85 (9)	82 (10)	0.084
BDI score	13.7 (2.3)	13.1 (2.6)	0.203

*Paired t test p value presented, except when Wilcoxon signed rank indicated.
†Data are non-normally distributed; median (IQR) and Wilcoxon signed rank p value presented.
CPFE, combined pulmonary fibrosis emphysema; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.

patient required oxygen supplementation at rest; 11 of 15 (73%) required ≥3 L of oxygen supplementation at rest. Table 2 shows the 6MWD improvements following 12 weeks of parenteral treprostinil therapy (mean 59 m; p<.001). Specifically, 8 of 15 patients improved by ≥57 m (range 57–150); 5 improved by ≥17 m (range 17–30); and 2 patients each declined by 10 m (figure 2). At 12 weeks, there were no significant differences in baseline oxygen requirements (see online supplementary repository figure S1) or oxygenation parameters by PPO either at rest on room air, at rest on 10 L FM, or at the completion of the 6MWD test on 10 L FM (table 2). Individual patient data are presented in the repository (see online supplementary table S3).

SF-36, UCSD SOB and BDI assessments

Patients had a statistically significant improvement in UCSD SOB and SF-36 MCS scores at the end of the study (p<0.05; table 3). When we assessed the clinical significance of these improvements, 77% and 50% had improvement ≥MID estimates for UCSD SOB and SF-36 MCS, respectively. Additionally, there was no significant change in SF-36 PCS and BDI (table 3) between baseline and 12 weeks. Individual patient data are presented in the repository (see online supplementary table S4).

Table 3 Quality of life and dyspnoea score changes using Short Form 36 (SF-36) and University of California San Diego Shortness of Breath (UCSD SOB) questionnaire

Quality of life/dyspnoea	Baseline N=15 Mean (SD)	12 weeks N=15 Mean (SD)	p Value*
UCSD SOB	87 (17.1)	73.1 (21)	0.002
SF-36 PCS aggregate	27.1 (5.8)	28 (8.8)	0.479
SF-36 MCS aggregate	38 (11)	44.2 (10.7)	0.005
Individual SF-36 domains			
Physical functioning†	10.0 (15.0)	25.0 (30.0)	0.003†
Role—physical	22.4 (6.6)	28.6 (9.4)	0.024
Bodily pain	47.6 (11.1)	39.4 (9.4)	0.049
General health	28.4 (7.6)	30.8 (7.6)	0.173
Vitality	36.9 (10.4)	41.9 (9.1)	0.026
Social functioning	28.0 (9.4)	33.9 (13.6)	0.014
Role—emotional	25.9 (13.2)	34.4 (11.1)	0.006
Mental health	42.4 (10.8)	45.3 (9.6)	0.150

*Paired t test p value presented, except when Wilcoxon signed rank indicated.
†Data are non-normally distributed; median (IQR) and Wilcoxon signed rank p value presented.
MCS, Mental Component Summary; PCS, Physical Component Summary.

Haemodynamics, BNP and Doppler echocardiography

All 15 patients had baseline mPAP ≥ 35 mm Hg; 10 (66%) had mPAP ≥ 40 mm Hg and 7 (47%) had mPAP ≥ 50 mm Hg. The transpulmonary gradient (TPG) at baseline was ≥20 mm Hg for all patients and ≥30 mm Hg in 12 of 15 (80%) patients. The average PVR was 698 ± 278 dyn s/cm^5, representing 44% of the mean systemic vascular resistance (SVR). The baseline PVR was ≥480 dyn s/cm^5 in all but three patients. Following 12 weeks of treprostinil, there was evidence of decreased RV afterload, as per significant reductions in mPAP, TPG, PVR, and increased pulmonary capacitance (table 4; see online supplementary repository figure S2). Right heart function improved, as per reductions in right atrial pressure and increased mixed venous oxygen saturation, cardiac index and SV index (table 4). Although the SBP fell by 11 mm Hg (124 ± 21 to 113 ± 13 mm Hg; p=0.028), the mean systemic arterial pressure was not altered and there was a downward trend in the PVR/systemic vascular resistance (SVR) ratio (p=0.060), suggesting proportionally greater pulmonary than systemic vasodilation. Importantly, there were no significant changes in resting heart rate, arterial oxygen content, or oxygen delivery. Individual patient data are presented in the repository (see online supplementary table S5).

The two-dimensional echocardiographic examination at baseline revealed normal left ventricular cavity size (LV end-diastolic dimension 4.1 ± 0.5 cm) and systolic function (LV ejection fraction 64 ± 6%), and Doppler evidence of normal left atrial pressure (transmitral Doppler E/e' ratio 5.4 ± 1.4). In contrast, subjects were noted to have severe RV dilatation (RV end-diastolic area 36.4 ± 5.2 cm^2), marked right-to-left displacement of the interventricular septum (systolic eccentricity index 1.7 ± 0.6) and moderate RV systolic dysfunction (tricuspid annular planar systolic excursion (TAPSE) 1.6 ± 0.5 cm; see online supplementary repository figure S3). Doppler estimated pulmonary artery systolic pressure at baseline was 72 ± 12 mm Hg. The RV outflow tract (RVOT) acceleration time was markedly reduced (66 ± 16 ms) and 100% of subjects showed evidence of systolic flow deceleration or 'notching' of the RVOT Doppler envelope. Of note, 85% of subjects showed evidence of both a TAPSE <2.0 cm and RVOT Doppler notching, consistent with afterload-dependent RV dysfunction at baseline.

Figure 3 illustrates that following 12 weeks of parenteral treprostinil treatment, there were significant reductions in RV size (p=0.021), less evidence of interventricular septal flattening

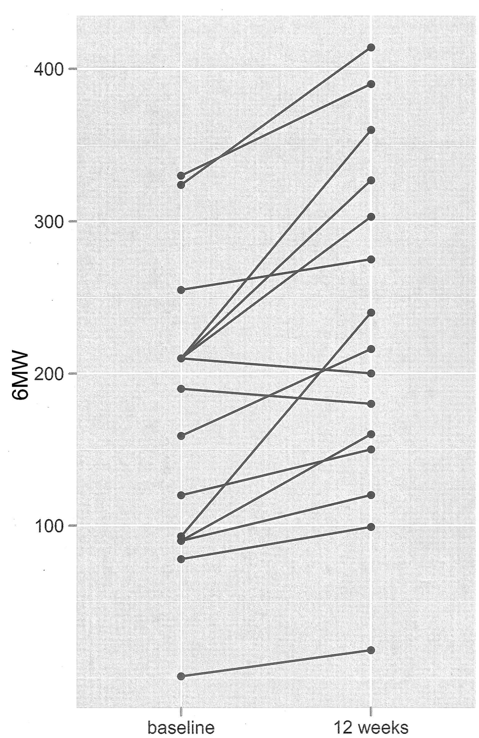

Figure 2 Individual 6 minute walk (6MW) distance responses to parenteral treprostinil at baseline and 12 weeks.

Table 4 Systemic and pulmonary haemodynamics and oxygenation at baseline compared with 12 weeks after parenteral treprostinil therapy

	Baseline N=15 Mean (SD)	12 weeks N=15 Mean (SD)	p Value*
Haemodynamics, mm Hg			
Right atrial pressure	9.5 (3.4)	6.0 (3.7)	<0.001
Mean pulmonary pressure	47.0 (8.0)	38.9 (13.4)	0.005
Pulmonary artery wedge pressure	12.5 (4.1)	10.5 (6.1)	0.247
Cardiac output (L/min)	4.3 (1.1)	4.9 (1.1)	0.042
Cardiac index (L/min/m^2)	2.3 (0.5)	2.7 (0.6)	0.017
PVR (dyn s/cm^5)	698 (278)	496 (229)	<0.001
Mixed venous O_2 saturation (%)	65 (7.2)	70.9 (7.4)	0.023
Haemoglobin (g/dL)	14.1 (2.1)	13.6 (2.2)	0.310
Arterial O_2 content (mL O_2/100 mL)	16.6 (3.1)	15.4 (3.6)	0.086
O_2 delivery (mL/min)†	6332 (2295)	7263 (5337)	0.246†
Pulmonary capacitance (mL/mm Hg)‡	1.28 (0.54)	1.64 (0.91)	0.013
RV pulsatility	0.94 (0.16)	1.04 (0.16)	0.010
Pulse pressure	44.1 (8.9)	40.3 (14.1)	0.182
Stroke volume (mL) †	51.8 (8.7)	61.8 (21.7)	0.031†
Stroke volume index	29.2 (6.7)	33 (7.3)	0.037
Systolic blood pressure†	125 (25)	109 (13)	0.028†
Mean arterial pressure	88.6 (15.8)	84.8 (9.4)	0.278
HR (beats/min)	79 (9.9)	80 (11.8)	0.490
Rs (dyn s/cm^5)	1575 (487)	1306 (357)	0.015
PVR/SVR	0.46 (0.13)	0.39 (0.15)	0.060
TPG	34.7 (8.7)	28.5 (10.3)	0.014
BNP (pg/mL)	558 (859)	228 (340)	0.004†

*Paired t test p value presented, except when Wilcoxon signed rank indicated.
†Data are non-normally distributed; median (IQR) and Wilcoxon signed rank p value presented.
‡Pulmonary capacitance = stroke volume/pulse pressure.
BNP, brain natriuretic peptide; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance; TPG, transpulmonary gradient.

(p=0.037), and improved RV systolic function (p=0.006). In parallel with haemodynamic and echocardiographic evidence of RV unloading, BNP levels fell significantly in subjects at 12-week follow-up (table 4).

Patient status

Of the 15 patients, 8 were actively listed for LT (figure 1). Of the 7 patients not offered LT, 5 died (mean ± SD) 504 ± 295 days after treprostinil initiation, while 2 patients remained alive 1059 and 1401 days after treprostinil initiation. After active listing, 7 patients were successfully bridged to LT which occurred at a median of 268 days (range 140–1379 days) after the baseline RHC and treprostinil initiation. The remaining listed patient died 272 days after treprostinil initiation.

DISCUSSION

The purpose of this investigation was to assess the effects of *chronic* parenteral treprostinil administration on right heart haemodynamics and echocardiographic function in a PF population referred for LT with an advanced PH phenotype, characterised by significantly increased PVR and RV dysfunction.[10] We studied this population either as a bridge to LT or to achieve clinical stabilisation in otherwise transplant ineligible patients at risk of clinical deterioration due to advanced PH and right heart dysfunction.[5 7 10] Significant improvements were demonstrated in right heart haemodynamics and echocardiographic function in response to chronic parenteral treprostinil infusion, without significant decrement in peripheral oxygen saturation, arterial oxygen content, or oxygen delivery.

At baseline, our subjects had a markedly elevated PVR, moderate to severe RV dysfunction, and thus abnormal coupling between the RV and pulmonary vascular load. In the context of significant RV–pulmonary artery uncoupling, RV afterload reduction leads to a predictable, afterload-dependent improvement in right heart function, as was seen in our cohort by way of improved haemodynamics and echocardiographic parameters.[11] These improvements in RV afterload and RV function (enhanced RV coupling) likely augmented the circulatory reserve of our patients, explaining their functional advantage and decreased dyspnoea.

The potential for worsening gas exchange with PH-targeted therapy deserves particular attention. We did not appreciate any significant hypoxaemia as assessed by PPO after treprostinil therapy, either at rest or after 6MWD testing. Importantly, pulmonary function (ie, degree of PF) remained unaltered during the study and did not likely confound these findings. Although arterial blood gases (ABG) were not obtained to confirm this finding, we can suggest a rationale based on the available literature. Prior work using multiple inert gas elimination technique (MIGET) has demonstrated a relatively preserved V-Q spectrum at rest, manifesting absent or mild resting hypoxaemia in patients with either WHO Group I pulmonary arterial hypertension (PAH)[12] or isolated PF.[13] Importantly, during exercise, the MIGET-derived V-Q spectrum remains preserved in both conditions, despite predictable widening of the alveolar-arterial gradient and hypoxaemia.[13–15] In PAH, this hypoxaemia is driven by a low mixed venous pO_2,[14] while in PF, hypoxaemia is characterised by a relative augmentation in diffusion abnormality, which in turn is further accentuated by low mixed venous oxygenation.[16] Consequently, a PH-targeted therapy that augments mixed venous oxygenation may be particularly desirable in a cohort of patients with PF and advanced PH to attenuate any predisposition for hypoxaemia at rest or during exercise.

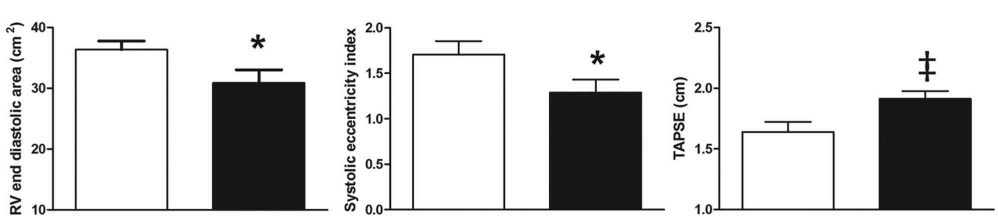

Figure 3 Bar graphs comparing indices of right ventricular size (RV end diastolic area), interventricular septal position (systolic eccentricity index), and RV systolic function (tricuspid annular planar systolic excursion) at baseline (open bars; n=15) and following 12 weeks of parenteral treprostinil (solid black bars; n=14), with error bars indicating SE. Paired t test results indicate significant improvements in RV size (p=0.021), interventricular septal flattening (p=0.037), and RV systolic function (p=0.006) indices from baseline to week 12. TAPSE, tricuspid annular planar systolic excursion.

The use of acute[15] or chronic[17–20] PH-targeted, non-prostanoid therapy does not appear to alter gas exchange in patients with PF without advanced PH during rest or exercise, which challenges the notion of predictable V-Q inequality and hypoxaemia as a direct result of underlying fibrotic lung disease. Despite this finding, acute parenteral prostanoid administration in patients with PF and advanced PH raises concern for predictable intrapulmonary shunt and hypoxaemia.[3 21] Interestingly, even patients with PAH (WHO Group I) demonstrated increased shunt by MIGET during acute parenteral prostanoid administration.[22] The question is whether this potential shunt and hypoxaemia are related to the parenteral route of administration or to the aggressive uptitration strategy routinely implemented when initiating parenteral prostanoid therapy.[23] In fact, prior studies evaluating acute parenteral prostanoid administration in PAH[22] and PF associated with advanced PH[3 21] employed this same aggressive uptitration protocol and report relatively worsened gas exchange, V-Q spectrum, and systemic haemodynamic data specifically at the prostanoid dose associated with intolerable adverse reaction and/or unacceptable haemodynamic deterioration. Similar and predictable V-Q inequality has also been demonstrated with other aggressively titrated, non-prostanoid vasodilators in patients with PAH.[24]

This approach may result in undesired physiology driven by decreased SVR, including reflex tachycardia, increased cardiac output (CO), systemic hypotension, and unchanged or increased PVR/SVR ratio. Comparable untoward physiology was recently demonstrated after riociguat therapy in patients with PF and advanced PH with resultant mild hypoxaemia.[25] While a patient with PAH may be able to tolerate an aggressive uptitration of parenteral prostanoid,[22] this strategy may place a patient with PF and advanced PH at risk of acute cardiopulmonary decompensation.[3] Consequently, a more gradual parenteral prostanoid uptitration approach may attenuate shunt physiology and subsequent hypoxaemia, especially if significant systemic vasodilation and the resulting abrupt rise in CO are avoided. Cardiac output may itself be associated with increased intrapulmonary shunt.[26] Based on the above, we surmise that a gentler uptitration of parenteral prostanoid, as employed in our study PF population with advanced PH, may lessen the potential for haemodynamic instability and/or hypoxaemia and rather parallel the chronic parenteral prostanoid administration haemodynamic and gas exchange data reported in WHO Group I PAH.

The inclusion of patients restricted to a severe baseline PH phenotype likely decreased the predisposition to arterial oxygen desaturation in response to treprostinil. Our subjects had a markedly elevated PVR and borderline reduced CO at baseline with evidence of significantly improved right heart function following treprostinil infusion, delineated by less septal bowing, a falling right atrial pressure, and improved CO. These salutary effects on right heart function may further optimise arterial oxygen content via enhanced mixed venous oxygen saturation.[16 27]

The improvement of 59 m in 6MWD following 12 weeks of parenteral treprostinil was noted in parallel with improvements in the UCSD SOB questionnaire and the SF-36 MCS, representing preliminary but encouraging findings. Recent independent studies in subjects with idiopathic pulmonary fibrosis (IPF) and Group I PAH suggested the minimally clinically important significant 6MWD difference to be 24–45 m and 25–38 m, respectively.[28 29] The augmentation in functional capacity seen in our subjects with PF-PH in response to treprostinil does not contravene prior studies reporting a lack of improvement in functional parameters in patients with PF treated with PH-targeted therapies.[17–19] Patients in these prior studies had no or mild PH, while our subjects had an average mPAP>45 mm Hg, a markedly elevated PVR, and degrees of RV dilatation and dysfunction comparable to severe WHO Group I PAH.[30]

These physiological differences are likely critical when considering the potential response to PH-targeted therapies, given that patients with advanced lung disease in the absence of advanced PH typically do not possess evidence of a circulatory limitation to exercise.[31 32] In contrast, patients with parenchymal lung disease (COPD or PF) and advanced PH demonstrate (in addition to their inherent ventilatory limitation) a circulatory limitation on exertion and an overall cardiopulmonary exercise stress test profile similar to isolated Group I PAH, with blunted oxygen pulse and marked ventilatory inefficiency (ie, increased V_E/V_{CO2}).[31 32] Importantly, the moderate degree of restrictive lung disease in our patient cohort may not have warranted consideration of LT, had it been isolated from the severe extent of superimposed PH. Interestingly, a recent post hoc analysis of a placebo-controlled randomised clinical trial in IPF[20] showed that the subgroup of patients with, compared with those without, RV dysfunction and RV hypertrophy improved their 6MWD in response to sildenafil.[33] In addition, the Royal Brompton group retrospectively reported a significant 6MWD improvement with sildenafil in a mixed interstitial lung disease population with pulmonary function and right heart haemodynamics similar to our experience.[2]

The combined observations of improved right heart function and stable arterial oxygen saturation in our PF-PH cohort after chronic parenteral treprostinil suggests the advanced PH phenotype may be critical when considering PH-targeted therapy, as it lends itself towards an increased likelihood of improved circulatory reserve and decreased risk of hypoxaemia. As such, an advanced PH phenotype in the context of chronic respiratory disease may be essential for predicting a beneficial response and minimising potential adverse effects of therapy.

LIMITATIONS

Limitations of this study include the heterogeneity of the PF population, variable background PH-targeted therapy, and the absence of ABG testing. The absence of a placebo arm is a particularly significant limitation; therefore, our findings must be confirmed with a randomised, placebo-controlled trial. At this point, the routine use of PH-targeted therapy in PF-PH is not recommended and should only be cautiously considered at specialised PH centres to avoid the serious potential for worsening cardiopulmonary status in this patient population. In addition, the explanation proposed for the lack of significant hypoxaemia with parenteral prostanoid in our PF-PH cohort remains speculative and requires further investigation. To address the limitation of multiple comparisons in the domains of pulmonary function, quality of life, and haemodynamics, we calculated that observed p values < 0.05 corresponded to a maximum q-value of 0.067, indicating that the proportion of significant findings attributable to false discovery is small. As such, we were reassured to see encouraging results in a real-world cohort of patients with PF referred for LT, characterised by an 'advanced PH and right heart dysfunction' phenotype. The lack of ABG testing is offset by stable arterial oxygen content, oxygen delivery, and oxygen saturation values at rest and 6MWD testing, following treprostinil therapy.

CONCLUSION

This open-label study suggests that gradual initiation and chronic administration of parenteral treprostinil therapy may

improve haemodynamics and right heart function without compromising systemic oxygenation in an advanced PH phenotype with RV dysfunction in the setting of PF. These findings are only hypothesis generating and require confirmation in a multicentre, randomised study design. Future studies of PH-targeted therapy for PF should focus on patients with PF with the combination of advanced PH and RV dysfunction, as these subjects may have greater capacity for benefit. Finally, given the high mortality inherent to this population, a future study may consider survival as an endpoint.

Author affiliations
[1]Thoracic Transplantation, Heart-Lung Institute, St Joseph Hospital & Medical Center, Phoenix, Arizona, USA
[2]Division of Rheumatology, Department of Medicine, University of Michigan, Ann Arbor, Michigan, USA
[3]Cardiovascular Division, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA
[4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[5]Department of Medicine Statistics Core, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[6]George Washington University, School of Medicine and Health Sciences, Washington, DC, USA
[7]Division of Radiology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[8]Cardiovascular Division, Temple University School of Medicine, Philadelphia, Pennsylvania, USA

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CHANGES IN RIGHT HEART HEMODYNAMICS AND ECHOCARDIOGRAPHIC FUNCTION IN AN ADVANCED PHENOTYPE OF PULMONARY HYPERTENSION AND RIGHT HEART DYSFUNCTION ASSOCIATED WITH PULMONARY FIBROSIS

DATA REPOSITORY FIGURES

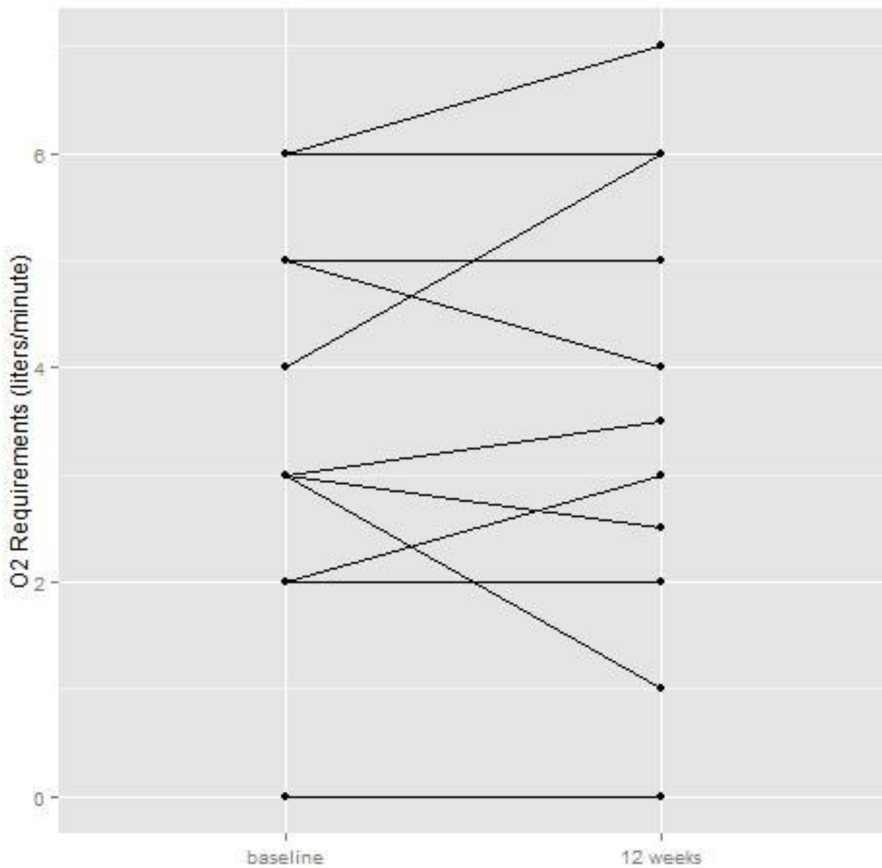

Figure 1: Individual oxygen requirements (liters/minute) at baseline and 12 weeks

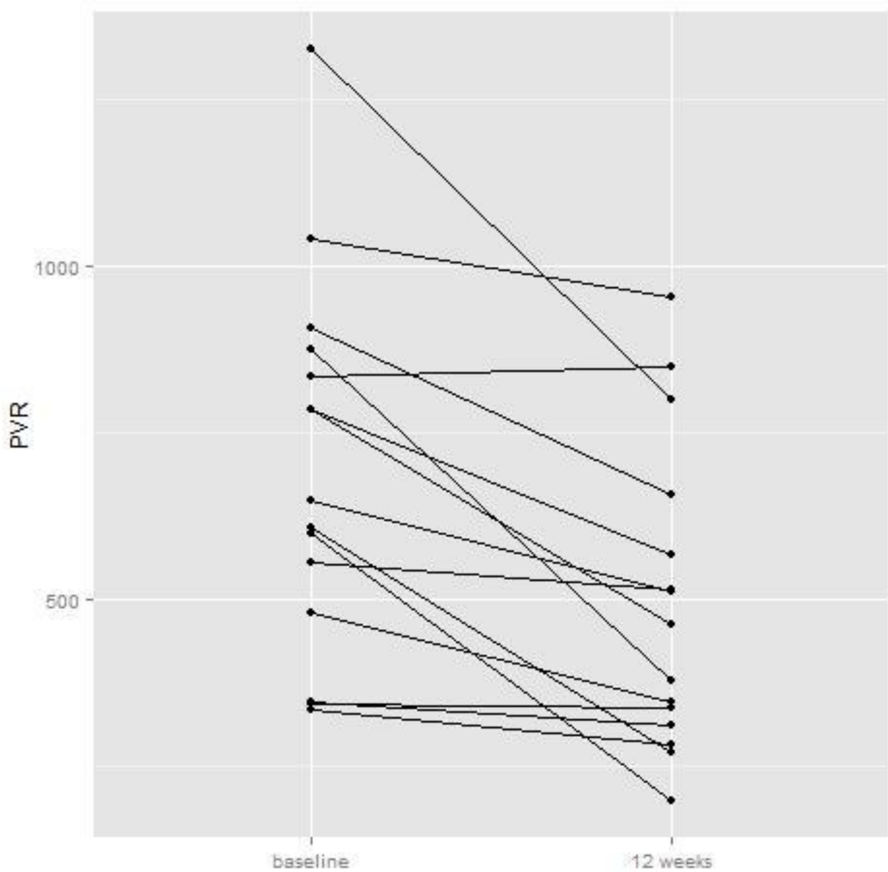

Figure 2: Individual pulmonary vascular resistance (PVR) calculations at baseline and 12 weeks

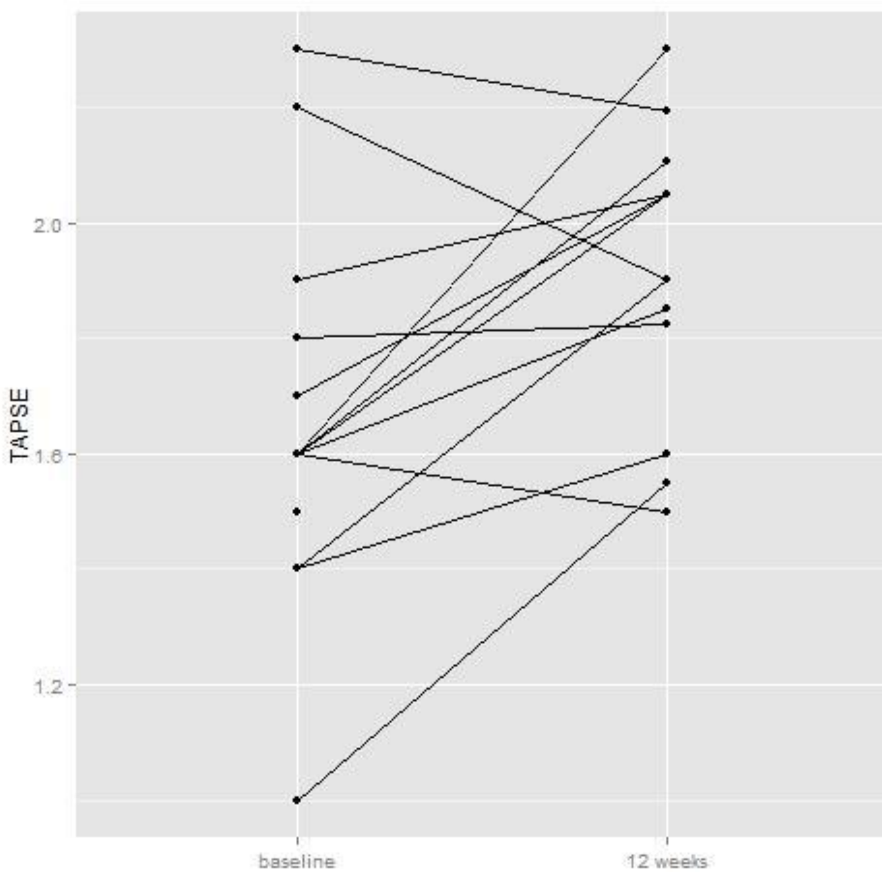

Figure 3: Individual tricuspid annular planar systolic excursion (TAPSE) measurements at baseline and 12 weeks

Repository:

Materials and Methods

Six minute walk distance (6MWD) and Oxygen Supplementation (OS) protocols:

Patients were seated for 10 minutes on room air and peripheral pulse oximetry (PPO) was recorded. A 10 liter oxygen face-mask (FM) was then applied and PPO was recorded after an additional 10 minutes at rest. 6MW testing was subsequently performed on a 10 liter oxygen FM with recording of the nadir oxygen saturation by PPO and the Borg Dyspnea Index (BDI) at the end of six minutes or at the end of the final ambulatory effort. The 6MW test was not interrupted or terminated for any degree of hypoxemia. No baseline 6MWD minimum was required for study entry. All RHCs and associated measurements were performed on a 10 liter oxygen FM.

Pulmonary function testing (PFT) and Doppler Echocardiogram (DE) protocols:

All measurements were made by 2 experienced echocardiographers (AF, PF) blinded to invasive hemodynamics and clinical data. Standard parameters were measured, including left ventricular ejection fraction, dimensions of the left atrium, left ventricular cavity and wall thickness, transtricuspid flow velocity, valvular regurgitation, transmitral E and A wave velocities, tissue Doppler of the mitral annulus, and inferior vena cava dimensions and collapse. In addition, parameters specific to pulmonary vascular disease and right ventricular size and function were assessed, including systolic eccentricity index, notching of the right ventricular outflow tract (RVOT) Doppler profile, acceleration time of this profile, RV two-dimensional area, and tricuspid annular plane systolic excursion (TAPSE). All measurements were made in accordance with American Society of Echocardiography guidelines and previously published literature,[1-3]

Dyspnea and Quality of Life Assessments:

A higher UCSD SOBQ score indicates more dyspnea with a minimally important difference (MID) of 5 points.[4] The BDI measures perceived breathlessness on a scale of 0 to 10 (maximum) with a MID of 1 point.[4]

The 8 SF-36 scales and the PCS and MCS scores are standardized to a mean of 50 and standard deviation of 10 in the US general population. MID estimates for SF-36 PCS and MCS are 2.5 points.[5]

Parenteral treprostinil titration protocol:

After treprostinil initiation at 2ng/kg/min and at any subsequent dose uptitration, vital signs including PPO were recorded every 15 minutes for 1 hour, then every hour for 3 hours, and subsequently every 4 hours until discharge. Arterial blood gases were not obtained in a standardized fashion. Inpatient treprostinil was increased by a maximum of 1ng/kg/min every 12 hours such that patients were discharged from the hospital at 48 hours on treprostinil doses of 3 to 5 ng/kg/min. After discharge, all attempts were made to uptitrate treprostinil by a maximum of 1ng/kg/min every 48 to 72 hours; however, the frequency and final dose of treprostinil was determined by the individual patient adverse reaction profile.[6]

High Resolution Computed Tomography (HRCT) Lung Parenchymal Scoring:

A likert scoring system was used based on percentage of area affected (0 = absent, 1= 1 to 5%, 2= 6 to 25%, 3= 26 to 50%, 4= 51 to 75% and 5= 76 to 100%) and assessed the extent of parenchymal abnormality involving three categories: groundglass opacity, lung fibrosis, and honeycombing. Each lobe and then both lungs were scored separately. Our scoring system is modified from earlier scoring systems reported by Kazerooni et al. and Kim et al.[7-8] In addition, both lungs were scored for total extent of ground glass opacity, fibrosis and/or honeycombing as being definitively less than 20%, definitively more than 20%, or indeterminate (10-30%).[9] In the few patients with combined pulmonary fibrosis and emphysema (CPFE), the extent of parenchymal abnormality was calculated without taking into account the extent of emphysema.

The following definitions were used for description of each of the radiographic findings: (1) ground-glass opacity; hazy parenchymal opacity with preservation of bronchial and vascular markings in the absence of reticular opacity, (2) architectural distortion/lung fibrosis; reticular opacification,

inter and intralobular septal thickening, traction bronchiectasis, or bronchiolectasis and architectural distortion, and (3) honeycombing; clustered air-filled cysts with well defined walls.[10]

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CHANGES IN RIGHT HEART HEMODYNAMICS AND ECHOCARDIOGRAPHIC FUNCTION IN AN ADVANCED PHENOTYPE OF PULMONARY HYPERTENSION AND RIGHT HEART DYSFUNCTION ASSOCIATED WITH PULMONARY FIBROSIS

DATA REPOSITORY TABLES

	Patients														
Patient Characteristics	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
NYHA	IV	IV	III	IV	III	III	III	IV	III	IV	IV	III	IV	III	III
Age in Years (at study entry)	69	75	67	84	60	44	40	71	34	68	71	65	65	65	69
Background Therapy	P	E/P	E	N	E	P	P	E/P	P	N	E/P	N	N	N	N
Clinical Subtype	IPF	IPF	IPF	IPF	NSIP-F	S	NSIP-F	CPFE	HP	CPFE	IPF	CPFE	IPF	IPF	IPF
Treprostinil dose at discharge	2	1	2	3	5	6	2	6	2	4	2	2	2	2	2
Treprostinil dose at 3 months	33	19	32	18	32	17	30	23	25	19	36	18	25	38	50
Treprostinil dose at 6 months	32	19	-	18	52	17	34	42	30	27	29	80	36	38	-
Treprostinil dose at 12 months	-	19	-	-	52	17	34	-	30	27	-	-	36	41	-
Treprostinil dose at last visit (i.e at time of lung transplant or at last clinic visit just before death)	36	19	32	18	52	17	34	55	29	16	29	80	56	26	58
Outcome	T	D	T	D	T	T	A	D	T	D	D	D	A	T	T
Time from treatment initiation to Outcome/Censor (days)	257	858	118	199	267	348	1498	311	1255	576	275	272	1351	606	148

Table 1: Patient demographics, underlying fibrotic lung disease clinical subtype, and background PH-targeted therapy

Background Endothelin receptor antagonist (E); Phosphodiesterase 5 inhibitor (P); No background therapy (N)
Clinical Subtypes: Idiopathic Pulmonary Fibrosis (IPF); NSIP-Fibrosis (NSIP-F); PF/Emphysema (CPFE); Chronic Hypersensitivity Pneumonitis (HP); Silicosis (S)
Outcome: Transplant (T); Death (D); Alive/Censor (A)

	Patients														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pathologic Confirmation	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	N	Y	Y	Y
< or > 20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%	>20%
Total Combined Score	5	4	3	3	5	3	3	3	5	3	5	4	4	5	4
Total Fibrosis RT Lung	2	4	2	3	2	1	1	3	3	2	1	3	3	3	2
Total Fibrosis LT Lung	2	4	2	3	2	1	1	3	3	2	0	3	3	3	2
Fibrosis RT Upper Lobe	1	3	2	2	2	1	1	2	3	1	0	2	2	3	2
Fibrosis RT Middle Lobe	2	3	2	2	3	1	1	2	3	1	1	3	3	3	2
Fibrosis RT Lower Lobe	2	4	1	3	3	1	1	3	3	2	0	3	4	3	1
Fibrosis LT Upper Lobe	1	3	2	2	2	1	1	2	3	1	0	2	2	3	2
Fibrosis LT Lower Lobe	2	4	1	3	3	1	1	3	3	2	0	3	4	3	2
Total GGO RT Lung	4	2	1	2	4	2	1	0	2	2	1	1	2	1	0
Total GGO LT Lung	4	1	1	2	4	2	1	0	2	2	0	1	2	1	0
GGO RT Upper Lobe	4	1	1	2	4	2	1	0	2	1	1	1	3	1	0
GGO RT Middle Lobe	4	1	1	2	4	2	1	0	2	1	1	1	2	1	0
GGO RT Lower Lobe	4	2	1	2	4	2	1	0	2	2	0	1	1	1	0
GGO LT Upper Lobe	4	2	1	2	4	2	1	0	2	1	0	1	2	1	0
GGO LT Lower Lobe	4	2	1	2	4	2	1	0	2	2	0	1	1	1	0
Total HC RT Lung	1	1	0	2	0	0	3	1	0	0	4	2	0	2	3
Total HC LT Lung	0	1	0	2	0	0	3	1	0	0	5	2	0	2	2
HC RT Upper Lobe	0	1	0	2	0	0	2	1	0	0	3	1	0	3	1
HC RT Middle Lobe	0	1	0	1	0	0	3	1	0	0	2	2	0	1	2
HC RT Lower Lobe	1	1	0	2	0	0	4	1	0	0	5	2	0	1	3
HC LT Upper Lobe	0	1	0	2	0	0	2	1	0	0	5	2	0	2	1
HC LT Lower Lobe	0	1	0	2	0	0	4	1	0	0	5	2	0	1	3

Table 2: Baseline high resolution computed tomography (HRCT) analysis of lung parenchymal abnormalities
RT: Right; LT: Left; GGO: Ground Glass Opacity; HC: Honeycombing; Ordinal Scoring System for Degree of Radiographic Involvement: 0= None; 1= 1 to 5%; 2= 6 to 25%; 3= 25 to 50%; 4= 51 to 75%; 5= >75%

	Week	Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pulmonary Function																
FVC, % Predicted	0	57	38	78	54	69	57	50	88	58	77	37	105	84	44	38
	12	66	33	82	62	74	64	54	66	63	82	38	94	84	44	41
FEV_1, % Predicted	0	58	48	74	70	74	43	51	90	49	71	43	95	70	46	49
	12	71	43	80	75	80	52	55	76	54	79	43	90	70	44	53
FEV_1/FVC	0	-	93	70	91	85	59	82	75	70	68	84	67	64	79	87
	12	81	96	73	85	109	65	82	85	70	71	82	71	64	76	88
TLC, % Predicted	0	71	45	78	58	51	89	64	78	75	84	59	98	84	55	55
	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DLCO, % Predicted	0	24	31	34	12	15	61	28	9	27	26	15	26	18	17	16
	12	29	-	-	14	19	61	33	22	23	29	12	22	18	14	25
FVC%/DLCO%	0	2.4	1.2	2.3	4.5	4.6	0.9	1.8	9.8	2.1	3	2.5	4	4.7	2.6	2.4
	12	2.3	-	-	4.4	3.9	1	1.6	3	2.7	2.8	3.2	4.3	4.7	3.1	1.6
Oxygen Flow (Liters/min)	0	2	5	3	6	6	4	0	5	3	3	6	2	6	5	2
	12	2	4	3.5	6	6	6	0	4	2.5	1	7	3	6	5	2
	26	2	4	-	6	6	8	3	4	2.5	3	8	6	6	5	-
	52	-	5	-	-	-	-	3	-	2	4	-	-	-	4	-
Six Minute Walk:																
6-minute walk distance (meters)	0	93	190	330	1	159	120	324	78	210	210	90	210	210	90	255
	12	240	180	390	18	216	150	414	99	360	303	120	200	327	160	275
	26	235	178	-	0	126	190	420	75	363	272	80	291	240	142	-
	52	-	165	-	-	-	-	507	-	333	275	-	-		80	-
Room Air % saturation (RA)	0	-	87	84	79	79	90	82	84	94	84	66	85	80	74	89
	12	-	85	79	78	65	86	92	80	94	84	61	88	79	64	80
10L face mask, % saturation	0	97	98	97	100	95	98	100	100	99	97	100	99	98	92	100
	12	100	94	95	96	100	97	100	99	100	98	99	100	97	86	100
10L face mask, % saturation nadir	0	93	75	76	89	81	97	92	80	98	82	77	87	85	70	95
	12	-	80	76	89	72	91	87	86	96	86	70	89	72	60	88
BDI Score	0	-	-	-	-	13	9	14	12	16	17	17	13	13	14	13
	12	-	17	13	13	13	9	14	13	13	17	15	11	13	8	15

Table 3: Pulmonary function testing, oxygen requirements, and 6 minute walk distance with Borg dyspnea index scores at baseline and end of study

	Week	Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Quality of Life/Dyspnea																
UCSD SOB	0	97	63	54	103	81	-	89	115	100	101	94	76	79	-	79
	12	67	77	32	101	70	-	68	104	71	88	72	43	52	97	81
SF36 PCS aggregate	0	-	15	87	33	56	21	52	.	17	16	22	40.4	20.2	13.2	63
	12	-	38	97	17	17	61	54	9	82	65	86	59.4	24.4	45.2	68
SF36 MCS aggregate	0	-	58	129	28	64	31	50	.	68	27	67	37.9	43.97	48.27	108.37
	12	-	80	137	48	112	42	74	63	108	72	79	73.63	56.53	68.53	106.3
Individual SF36 Domains																
Physical Functioning	0	-	10	25	0	0	0	25	-	15	0	0	15	10	0	20
	12	-	25	35	0	0	100	30	0	45	15	15	50	5	15	30
Role-Physical	0	-	0	200	0	100	0	125	-	0	0	0	25	0	0	100
	12	-	100	300	0	0	100	125	0	200	200	275	100	0	100	100
Bodily Pain	0	-	32	100	100	100	52	52	-	41	42	62	62	61	31	100
	12	-	12	52	32	31	50	41	22	74	31	62	52	62	41	100
General Health	0	-	10	52	45	45	20	30	-	10	25	20	45	0	10	25
	12	-	25	42	35	25	10	30	5	25	40	30	40	15	25	40
Vitality	0	-	25	60	20	35	35	30	-	20	15	30	55	30	25	70
	12	-	30	55	20	30	45	45	20	65	40	50	55	40	45	70
Social Functioning	0	-	63	88	13	25	38	38	-	25	0	38	37.5	12.5	25	37.5
	12	-	75	100	13	38	0	63	0	88	25	63	62.5	25	50	37.5
Role-Emotional	0	-	133	367	0	133	0	100	-	233	67	200	0	133.33	133.33	333.33
	12	-	200	400	100	400	100	167	233	300	200	200	166.67	166.67	166.67	300
Mental Health	0	-	60	80	64	84	64	52	-	52	28	48	52	44	48	76
	12	-	68	88	72	68	56	64	56	60	56	52	44	36	56	84

Table 4: Quality of life and dyspnea score changes using Short Form 36 (SF-36) and University of California San Diego shortness of breath questionnaire
PCS: Physical Component Summary; MCS: Mental Component Summary

	Week	Patients														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Hemodynamics, mmHg																
Right atrial pressure (RA)	0	11	12	18	8	8	9	8	14	11	7	6	10	10	5	6
	12	5	9	11	1	8	11	0	8	9	4	6	8	2	2	3
mean Pulmonary Pressure (mPA)	0	49	56	59	40	50	55	46	53	52	40	56	42	36	38	36
	12	20	51	51	30	48	70	29	49	35	31	47	35	22	32	34
Pulmonary Artery Wedge Pressure	0	18	12	18	6	10	15	15	5	14	10	9	12	14	18	11
	12	10	25	15	7	9	20	4	7	15	6	12	8	4	10	5
Cardiac Output (L/min)	0	3.73	3.75	3.87	3	4.1	3.07	7.2	2.9	5	3.7	4.5	5	5.7	4.6	3.6
	12	4	5.5	6.23	2.8	5.5	4.2	5.9	4.2	5.9	3.9	3.3	6.2	5.1	5.7	4.5
Cardiac Index ($L/min/m_2$)	0	2.2	2.25	2.02	1.75	2.3	1.68	3.36	1.31	2.7	1.96	2.6	2.8	3.05	2.2	2.1
	12	2.63	3.35	3.31	1.6	3.13	2.28	2.75	2.28	3.17	2.16	1.92	3.46	2.8	3.54	2.6
PVR (dyn sec/cm^5)	0	600	874	786	906	784	1040	344	1324	608	649	835	480	336	347	555
	12	200	378	462	657	567	952	338	800	271	512	848	348	282	313	515
Mixed Venous O_2 Saturation (%)	0	60	61	65	60	72	69	-	49	-	65	75	69	.	69	.
	12	66	68	77	69	79	58	-	59	76	79	72	80	.	72	66
Hemoglobin (g/dL)	0	10.1	12.8	17.1	14.5	12.5	16.1	16.4	13	17.3	15	11.2	14	12.5	14.5	13.8
	12	10.8	13	16.5	13.8	13.1	12.9	14.9	11.3	14.6	18.7	10.1	15	12.9	14.4	11.8
Arterial O_2 Content (mL O2/100mL)	0	-	1547.9	1996.6	1592.25	1372.63	2014.11	1869.27	1517.88	2260.42	1751.4	1027.49	1654.1	1390	1491.47	1707.2
	12	-	1535.95	1811.87	1496.2	1183.59	1542.07	1905.41	1256.56	1907.64	2183.41	856.38	1834.8	1416.55	1281.02	1312.16
O_2 Delivery (mL/min)	0	-	5804.64	7726.83	4776.74	5627.76	6183.32	13458.8	4401.85	11302.1	6480.18	4623.7	8270.5	7923	6860.76	6145.91
	12	-	8447.73	11287.9	4189.35	6509.72	6476.68	11241.9	5277.55	11255.1	8515.31	2826.05	11375.8	7224.4	7301.84	5904.72
Pulmonary Capacitance (mL/mmHg)	0	1.15	1.25	1.06	0.87	1.06	0.56	2.5	0.96	1.09	1.27	0.85	1.79	2.06	1.6	1.51
	12	3.03	1.34	1.84	1.17	1.16	0.63	3.29	1	2.45	1.54	0.62	1.75	3.8	1.78	1.6
RV Pulsatility	0	0.92	0.71	0.78	1.35	0.98	1.07	0.87	0.85	0.92	0.9	1.07	0.74	0.92	1.05	0.97
	12	1	0.902	0.9216	1.4	1.125	0.9714	0.9655	1.0204	0.8286	1.0323	1.234	1.0571	0.7727	1.25	1.0588
Pulse Pressure	0	45	40	46	54	49	59	40	45	48	36	60	31	33	40	35
	12	20	46	47	42	54	68	28	50	29	32	58	37	17	40	36
Stroke Volume (mL)	0	51.81	50	48.99	46.88	51.9	33.01	100	43.28	52.08	45.68	51.14	55.56	67.86	63.89	52.94
	12	60.61	61.8	86.53	49.12	62.5	42.86	92.19	50	71.08	49.37	35.87	64.58	64.56	71.25	57.69
Stroke Volume Index	0	30.56	30	25.57	27.34	29.11	18.06	46.67	19.55	28.13	24.2	29.55	31.11	36.31	30.56	30.96
	12	35.75	37.08	45.16	28.66	35.06	23.45	43.02	22.59	38.39	26.15	20.72	36.17	34.54	34.08	33.74
Systolic Blood Pressure	0	125	160	124	136	109	119	-	90	128	135	159	110	135	91	120
	12	107	147	101	103	106	113	-	100	126	109	127	105	108	118	116
Mean Arterial Pressure	0	75	114	91	98	68	96	-	70	92	105	113	83	92	73	70
	12	81	108	87	75	76	90	-	82	94	85	94	75	75	81	84
HR (beats/minute)	0	72	75	79	64	79	93	72	67	96	81	88	90	84	72	68
	12	66	89	72	57	88	98	64	84	83	79	92	96	79	80	78
Rs (dyn sec/cm^5)	0	1222.52	2176	1509.04	2453.33	1131.71	2110.75	-	1793.1	1248	2054.05	1848.89	1136	1094.74	956.52	1311.11
	12	1420	1207.27	924.56	1942.86	974.55	1333.33	-	1428.57	1071.19	1620.51	1987.88	864.52	1113.73	996.49	1404.44
PVR/Rs	0	0.49	0.4	0.52	0.37	0.69	0.49	-	0.74	0.49	0.32	0.45	0.42	0.31	0.36	0.42
	12	0.14	0.31	0.5	0.34	0.58	0.71	-	0.56	0.25	0.32	0.43	0.4	0.25	0.31	0.37
TPG	0	31	44	41	34	40	40	31	48	38	30	47	30	22	20	25

	12	10	26	36	23	39	50	25	42	20	25	35	27	18	22	29
BNP (pg/mL)	0	352	368	858	839	171	125	21	3470	20	66	250	408	54	554	810
	12	150	31	644	288	77	213	20	1310	20	123	20	102	20	165	244
	26	84	64	-	251	165	113	20	2030	20	20	240	189	21	102	-
	52	-	39	-	-	-	-	20	-	20	81	-	-	-	607	-

Table 5: Systemic & pulmonary hemodynamics and oxygenation at baseline compared to 12 weeks after parenteral treprostinil therapy

PVR: pulmonary vascular resistance; pulmonary capacitance = (stroke Volume/pulse pressure); Rs: systemic vascular resistance
TPG: transpulmonary gradient)
BNP: brain natriuretic peptide

EXHIBIT 23

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

ABSTRACT

BACKGROUND
No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

METHODS
We enrolled patients with interstitial lung disease and pulmonary hypertension (documented by right heart catheterization) in a multicenter, randomized, double-blind, placebo-controlled, 16-week trial. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total, 72 μg) four times daily, or placebo. The primary efficacy end point was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary end points included the change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

RESULTS
A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; $P<0.001$). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; $P<0.001$). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; $P=0.04$ by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

CONCLUSIONS
In patients with pulmonary hypertension due to interstitial lung disease, inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with placebo. (Funded by United Therapeutics; INCREASE ClinicalTrials.gov number, NCT02630316.)

From Brigham and Women's Hospital, Boston (A.W.); the University of South Florida, Tampa (R.R.-J.), and St. Vincent's Lung, Sleep, and Critical Care Specialists, Jacksonville (A.B.) — both in FL; the University of Minnesota, Minneapolis (T.T.); St. Vincent Medical Group, Indianapolis (A.R.); the Carl and Edyth Lindner Research Center at the Christ Hospital, Cincinnati (P.E.); University of California Davis Medical Center, Sacramento (R. Allen), and Cedars–Sinai, Los Angeles (V.T.); Arizona Pulmonary Specialists, Phoenix (J.F.); the Medical University of South Carolina, Charleston (R. Argula); United Therapeutics Corporation, Silver Spring, MD (P.S., K.R., C.D., L.P., H.B.); and Inova Fairfax Hospital, Falls Church, VA (S.D.N.). Address reprint requests to Dr. Nathan at the Advanced Lung Disease and Lung Transplant Program, Inova Heart and Vascular Institute, 3300 Gallows Rd., Falls Church, VA 22042, or at steven.nathan@inova.org.

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Precapillary pulmonary hypertension is defined as an elevation in mean pulmonary arterial pressure and pulmonary vascular resistance.[1] In the World Health Organization (WHO) classification of pulmonary hypertension, precapillary pulmonary hypertension due to lung disease is classified as group 3. The most common lung diseases associated with group 3 pulmonary hypertension are chronic obstructive pulmonary disease and interstitial lung disease.

Pulmonary hypertension has been reported in up to 86% of patients with interstitial lung disease and is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death.[2-4] Despite the global prevalence and poor clinical course of pulmonary hypertension due to interstitial lung disease, there are currently no approved therapies for these patients. Although data are limited, therapies approved for group 1 pulmonary hypertension (pulmonary arterial hypertension) have been used to treat group 3 pulmonary hypertension.[5] Previous studies of vasodilator therapies have shown conflicting results. The largest trial to date evaluated the soluble guanylate cyclase stimulator riociguat in a patient population with group 3 pulmonary hypertension and was stopped early owing to serious harm.[6]

Treprostinil is a stable analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.[7] An inhaled formulation of treprostinil was previously shown to improve exercise capacity after 12 weeks of therapy in patients with group 1 pulmonary hypertension.[8] Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension.[9-12] Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.

METHODS

TRIAL DESIGN AND OVERSIGHT

INCREASE was a multicenter, randomized, double-blind, placebo-controlled trial. The steering committee (the first author and last two authors), in collaboration with the trial sponsor (United Therapeutics), designed the trial and oversaw its conduct. The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating site. The trial was monitored by an independent data and safety monitoring committee and was conducted in accordance with Good Clinical Practice guidelines. A full list of trial personnel, including the investigators and trial committees, is provided in Section S1 in the Supplementary Appendix, available at NEJM.org.

The collection, management, and analysis of the data were performed by the sponsor according to a prespecified statistical analysis plan (provided in the protocol). An independent academic statistician reviewed the statistical analysis plan and confirmed the primary efficacy analyses. Authors had independent access to the data and authority to conduct and confirm statistical analyses. All manuscript drafts were written by the steering committee and authors affiliated with the sponsor and were reviewed and approved by all the authors. The authors assume responsibility for the accuracy and completeness of the data, as well as for the fidelity of the trial to the protocol.

TRIAL POPULATION

The trial population consisted of patients 18 years of age or older in whom interstitial lung disease was diagnosed on the basis of evidence of diffuse parenchymal lung disease on computed tomography of the chest (not centrally adjudicated) performed within 6 months before randomization. Confirmation of group 3 pulmonary hypertension by right heart catheterization within 1 year before randomization was required. Group 3 pulmonary hypertension was defined by pulmonary vascular resistance of more than 3 Wood units, pulmonary capillary wedge pressure of 15 mm Hg or lower, and mean pulmonary arterial pressure of 25 mm Hg or higher. Patients with group 3 pulmonary hypertension due to connective tissue disease were also required to have a baseline forced vital capacity of less than 70%. Eligible patients also had to walk at least 100 m during a 6-minute walk test. Patients receiving drug treatment (i.e., pirfenidone or nintedanib) for their underlying lung disease were required to have been receiving a stable dose for at least 30 days before undergoing randomization. Patients re-

ceiving approved therapy for pulmonary arterial hypertension within 60 days before randomization were not eligible for enrollment. A complete list of trial enrollment criteria is provided in Section S2. Written informed consent was obtained from all the patients.

TRIAL PROCEDURES

Within 30 days after screening, eligible patients were randomly assigned in a 1:1 ratio to receive inhaled treprostinil (Tyvaso, United Therapeutics) or placebo in a double-blind manner. Randomization, based on permuted blocks, was stratified by baseline 6-minute walk distance (≤350 m vs. >350 m) and was implemented through an interactive Web-response system.

Inhaled treprostinil (0.6 mg per milliliter) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 μg per breath. Placebo was administered similarly as a visually identical solution. The first dose of trial drug (3 breaths) was administered in the clinic, followed by at least a 1-hour observation period. The dose of treprostinil or placebo was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maximum dose of 12 breaths four times daily. Investigators adjusted the dose on an individual patient basis to achieve the maximum tolerated dose leading to functional improvement.

TRIAL ASSESSMENTS

The 6-minute walk test was performed and laboratory data were obtained at baseline and at weeks 4, 8, 12, and 16, or at the time of early discontinuation of treprostinil or placebo. Each 6-minute walk test was performed 10 to 60 minutes after the most recent dose of active drug or placebo, which is the time of peak plasma treprostinil exposure. (A description of the procedure for the 6-minute walk test is provided in Section S3.) A trough test was performed at week 15 at least 4 hours after the participant received a dose of treprostinil or placebo and at least 24 hours before the week 16 test. Pulse oximetry was performed immediately before, during, and after each 6-minute walk test. Measurement of N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and pulmonary function tests were performed at baseline and at weeks 8 and 16 (or at early discontinuation) after the patients recovered from the 6-minute walk test. The St. George's Respiratory Questionnaire (SGRQ), a quality-of-life measure, was completed at baseline and week 16 or at the time of early discontinuation.

OUTCOME MEASURES

The primary end point of the trial was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary efficacy end points were analyzed in the following hierarchical testing order: the change in NT-proBNP level from baseline to week 16, the time to clinical worsening, the change in 6-minute walk distance at peak plasma treprostinil level at week 12, and the change in 6-minute walk distance at trough treprostinil level at week 15. The time to clinical worsening was evaluated from the time of randomization until the patient's withdrawal from the trial and was defined as the time until the occurrence of any one of the following events: hospitalization for a cardiopulmonary indication, a decrease in 6-minute walk distance greater than 15% from baseline that was directly related to the disease under study at two consecutive visits and at least 24 hours apart, death from any cause, or lung transplantation.

Exploratory end points were the changes in peak 6-minute walk distance at weeks 4 and 8, quality of life as measured with the use of the SGRQ at week 16, and the distance–saturation product (calculated by multiplying the total distance walked by the lowest oxygen saturation measurement during the 6-minute walk) at week 16. Safety end points included adverse events, abnormal laboratory results, oxygenation as measured by pulse oximetry (Sp_{O_2}) and supplemental oxygen requirement, changes in pulmonary function test results, hospitalization for a cardiopulmonary indication, and investigator-reported exacerbations of underlying lung disease, defined as acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality. A full list of trial end points is provided in Section S4.

STATISTICAL ANALYSIS

Original estimates suggested that with 266 patients randomly assigned in a 1:1 ratio to receive

inhaled treprostinil or placebo, the trial would have at least 90% power at a significance level of 0.05 (two-sided) to detect a between-group difference of 30 m in the change in peak 6-minute walk distance from baseline at week 16, assuming a standard deviation of 75 m. To account for approximately 15% of participants discontinuing the trial, 314 patients would need to be enrolled.

For the primary efficacy analysis, the change in 6-minute walk distance was analyzed by mixed-model repeated-measures methods, under the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed by means of a multiple imputation approach with a multivariate normal imputation model according to the Markov chain Monte Carlo method. The imputation model included treatment group, all scheduled visits, the patient's sex, and the patient's age at randomization. If the result for the primary efficacy end point was significant, secondary efficacy end points were to be evaluated according to a hierarchical testing procedure. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects for secondary efficacy end points. Additional details of the statistical methods are provided in Section S5.

RESULTS

PATIENTS

Of 462 patients screened for eligibility, 326 were enrolled at 93 centers from February 3, 2017, through August 30, 2019, and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients) (Fig. 1). Reasons for screening failure for the 136 patients who were excluded are shown in Table S1. Baseline characteristics were similar in the two groups (Table 1). The mean age of the patients was 66.5 years, 46.9% were female, and the most common diagnosis was idiopathic interstitial pneumonia (in 44.8%). Baseline test data are provided in Table S2. At baseline, the mean 6-minute walk distance was 259.6 m, the mean pulmonary vascular resistance was 6.2 Wood units, and the mean NT-proBNP level was 1832.9 pg per milliliter.

EXPOSURE AND FOLLOW-UP

Patients in the treprostinil group took a median of 11 breaths from the inhaler (66 μg) at each of four daily sessions at week 12 and 12 breaths (72 μg) per session at week 16. The percentage of patients in this group who took 10 to 12 breaths (60 to 72 μg) per session was 57.0% at week 12 and 57.8% at week 16. Patients in the placebo group took a median of 12 breaths from the inhaler per session at weeks 12 and 16.

The date of the database lock was February 18, 2020. Forty patients assigned to receive inhaled treprostinil (24.5%) and 38 assigned to placebo (23.3%) discontinued the assigned regimen prematurely. These patients were encouraged to remain in the trial and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued participation in the trial. The reasons for discontinuation are shown in Figure 1.

PRIMARY END POINT

Mean within-group changes in the 6-minute walk distance are shown in Figure 2. Mixed-model repeated-measures analysis showed that the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001) (Table 2 and Fig. S1). Similar effects were observed across subgroups, including subgroups defined by disease cause and severity (as measured by baseline 6-minute walk distance), baseline hemodynamics, and dose group (Fig. S2). In addition, the between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41; P<0.001) (Fig. S3).

SECONDARY AND EXPLORATORY END POINTS

Patients assigned to inhaled treprostinil, as compared with those assigned to placebo, showed significant improvements in each of the secondary end points (Table 2). The NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with

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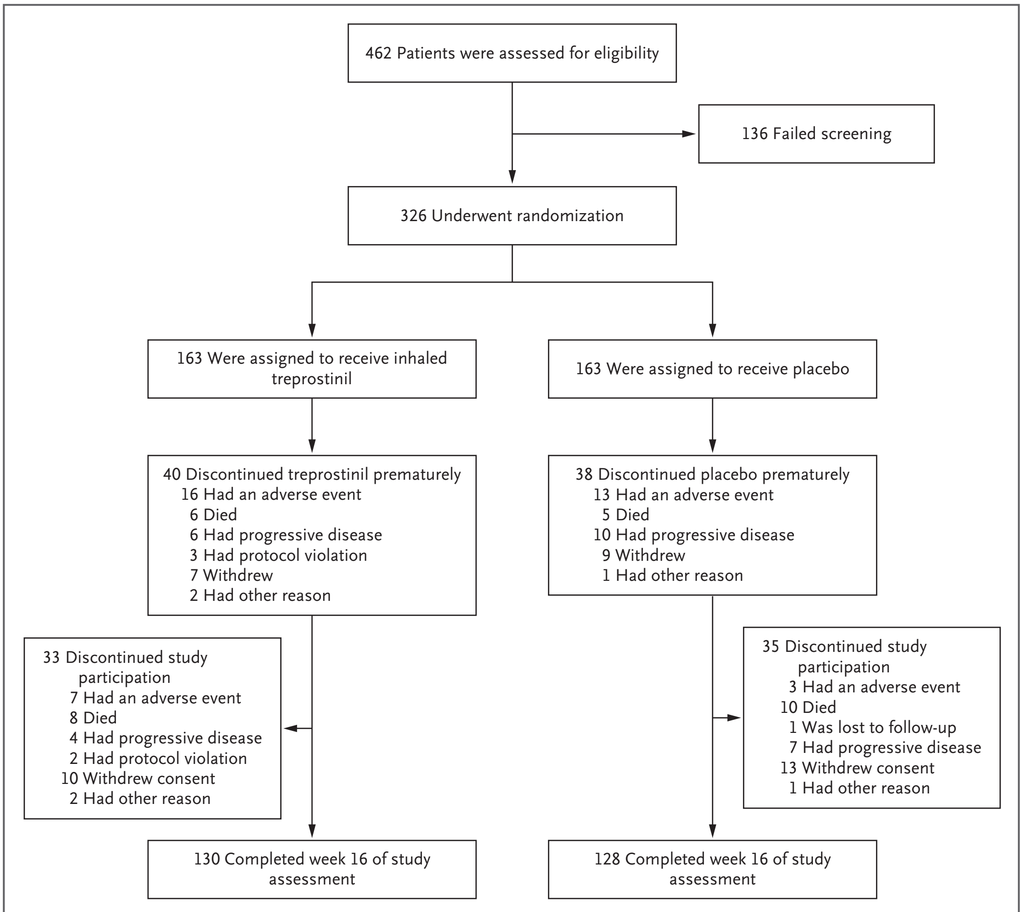

Figure 1. Screening, Randomization, and Follow-up.

Of 462 patients screened for eligibility, 326 patients underwent randomization and received at least one dose of the assigned treprostinil or placebo (included in the intention-to-treat and safety populations). Reasons for screening failure (136 patients) are shown in Table S1. Of the patients who underwent randomization, 40 patients in the treprostinil group and 38 in the placebo group discontinued the assigned regimen prematurely. These patients were not withdrawn from the trial but were encouraged to remain and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued trial participation before week 16.

placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001) (Fig. S4). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test) (Fig. S5). The least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group (P<0.001), and the change from baseline to week 15 in trough 6-minute walk distance was 21.99 m greater in the treprostinil group (P=0.004). There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16 (Tables S3 and S4).

SAFETY END POINTS

The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea (Table 3). Most of these

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen — no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy — no. (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

* Plus–minus values are means ±SD. Additional patient characteristics at baseline are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the patient.

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events were of mild-to-moderate intensity. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo (Table S5). No serious adverse events were reported significantly more frequently in the treprostinil group than in the placebo group. A full list of serious adverse events is provided in Table S5.

Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P=0.02 by Fisher's exact test). Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%]; P=0.41). Inhaled treprostinil had no deleterious effect on any pulmonary function test variable during the trial (Table S6). There were no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the trial period (Tables S7 and S8).

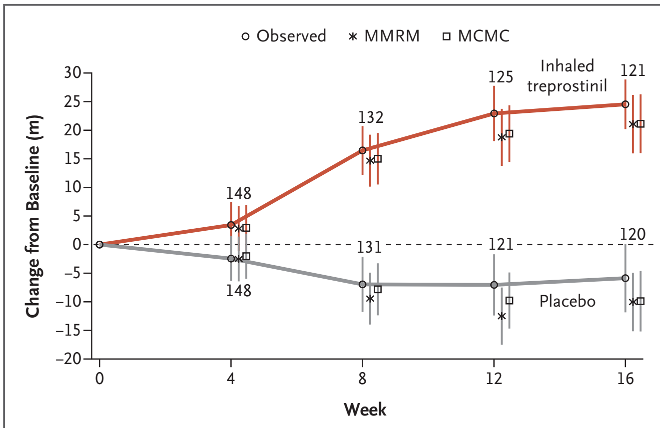

Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

Shown are mean (±SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

DISCUSSION

Pulmonary hypertension frequently complicates the treatment of patients with interstitial lung disease and is associated with worse functional status, greater need for supplemental oxygen, and worse outcomes.[3,13] In the INCREASE trial, patients treated with inhaled treprostinil had significant improvements in exercise capacity, as evidenced by changes in the 6-minute walk distance. Treatment with inhaled treprostinil was also associated with a lower risk of clinical worsening than that in patients who received placebo, as well as reductions in NT-proBNP levels and fewer exacerbations of underlying lung disease, over the 16-week treatment period. The safety profile of inhaled treprostinil observed in this vulnerable patient population was similar to that reported in previous studies. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. The use of inhaled treprostinil was not associated with any decrement in lung function.

Patients with group 3 pulmonary hypertension are often treated with systemic pulmonary vasodilators, which are currently approved only for treatment of group 1 pulmonary hypertension. However, there is concern that such agents could worsen ventilation–perfusion matching in patients with group 3 pulmonary hypertension. Inhaled agents have the advantage of preferentially redirecting blood flow to the best-ventilated lung units, thus reducing the risk of ventilation–perfusion mismatching.[9,14] Indeed, a retrospective study of inhaled treprostinil in patients with group 3 pulmonary hypertension showed that such patients had improvements in functional class and 6-minute walk distance without any adverse effect on peripheral oxygen saturation, reinforcing the concept of unchanged or even improved ventilation–perfusion matching with inhaled treprostinil.[10] Similarly, in the current trial, we found no evidence of worsened oxygenation, which further allays concerns about ventilation–perfusion mismatching.

The INCREASE trial was not without its limi-

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Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

* Plus–minus values are means ±SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.

† The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.

‡ This is a least-squares mean difference between the groups.

§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.

¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.

‖ This is the treatment ratio, which is the ratio of ratios between two treatment groups.

** This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

†† The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

tations. The trial was of short duration, and 21% of the patients discontinued the trial prematurely (before week 16). In addition, events of clinical worsening and exacerbation of underlying lung disease were investigator-reported and not adjudicated by an independent review committee. Finally, the size of the favorable treatment effect on the 6-minute walk distance with inhaled treprostinil is similar to estimates of the minimum clinically important difference for this test in patients with pulmonary disease (21.7 to 37 m in a study by Nathan et al., and 24 to 45 m in a study by du Bois et al.).[15,16]

This study showed that among patients with

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Table 3. Summary of Adverse Events.

Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

* P values were calculated with the use of Fisher's exact test.
† A list of serious adverse events is shown in Table S5.
‡ Shown are the most frequently occurring adverse events occurring in more than 10% of patients in either group in the safety population, which comprised all patients who underwent randomization and received at least one dose of treprostinil or placebo.

pulmonary hypertension due to interstitial lung disease, treatment with inhaled treprostinil improved exercise capacity as shown by improvement in the 6-minute walk distance through the end of the 16-week treatment period. In addition, treatment with inhaled treprostinil was associated with a lower risk of clinical worsening than that with placebo, a reduction in NT-proBNP levels, and fewer exacerbations of underlying lung disease.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med 2021;384:325-34. DOI: 10.1056/NEJMoa2008470

Table of Contents

1. List of Investigators and Trial Committees

The INCREASE Investigators are as follows:

Roblee Allen, MD, University of California, Davis Medical Center; Hassan Alnuaimat, MD, University of Florida Clinical Research Center; MaryEllen Antkowiak, MD, Vermont Lung Center; Alvaro Aranda, MD, Auxilio Mutuo Hospital; Rahul Argula, MD, Medical University of South Carolina; Francis J Averill, MD, JD, St. Francis Sleep Allergy and Lung Institute; Rana Awdish, MD, Henry Ford Health System; Remzi Bag, MD, University of Chicago Medical Center; Abubakr A. Bajwa, MD, St. Vincent's Lung, Sleep, and Critical Care Specialists; Vandana Kavita Seeram, MD, Abubakr A. Bajwa, MD, University of Florida College of Medicine; Vijay Balasubramanian, MD, University of California San Francisco – Fresno; Christopher Barnett, MD, MedStar Washington Hospital Center; Sonja Bartolome, MD, UT Southwestern Medical School; Himanshu Bhardwaj, MD, OU Medical Center; Robert C Bourge, MD, The Kirklin Clinic of UAB Hospital; Jeffrey Robinson, MD, John Butler, MD, The Oregon Clinic-Pulmonary, Critical Care & Sleep Medicine-West; Andrew Kolodziej, MD, Ketan Buch, MD, University of Kentucky Medical Center; Todd M. Bull, MD, University of Colorado Hospital – Cardiac and Vascular Center; Charles Burger, MD, Mayo Clinic Florida; Hector Cajigas, MD, Northwestern University School of Medicine; Michael Campos, MD, Miami Veterans Affairs Medical Center; Amy Case, MD, Piedmont – Georgia Lung Associates; Roxana Sulica, MD, Rany Condos, MD, NYU Langone Health; David De La Zerda, MD, University of Miami Pulmonary Research Center; Shilpa DeSouza, MD, Winthrop-University Hospital, Clinical Trials Center; Adrian G. DiVittorio, MD, IMC - Diagnostic & Medical Clinic; Hilary M. DuBrock, MD, MMSc, Mayo Clinic; Michael S. Eggert, MD, Sentara Norfolk General Hospital; Sherif G. El Bayadi, MD, Pulmonary Health Physicians, PC; Jean Elwing, MD, UC Health; Peter J. Engel, MD, The Carl and Edyth Lindner Research Center at The Christ Hospital; Karen A. Fagan, MD, University of South Alabama; Peter S. Marshall, MD, Wassim Fares, MD, Yale New Haven Hospital; Jeremy P. Feldman, MD, Arizona Pulmonary Specialists, Ltd.; Micah Fisher, MD, The Emory Clinic; Hubert James Ford III, MD, University of North Carolina Hospitals; Dr. Sandeep Sahay, MD, Adaani Frost, MD, Houston Methodist; James Patrick Gagermeier, MD, Loyola University Medical Center; Sivagini Ganesh, MD, University of Southern California, Health Sciences Campus; Hernando Garcia, MD, Texas Tech University, Health Sciences Center at El Paso; Alicia Gerke, MD, University of Iowa Hospitals & Clinics; Reda Ebeid Girgis, MD, Spectrum Health Heart & Lung Specialized Care Clinic; Jeffrey Golden, MD, University of California San Francisco; Maria Giovanna Trivieri, MD, Radha Gopalan, MD, Mount Sinai Medical Center; John Kingrey, MD, Janardhana Gorthi, MD, INTEGRIS Baptist Medical Center; Dana McGlothlin, MD, Sachin Gupta, MD, Kaiser Permanente; Antoine Hage, MD, Cedars - Sinai Medical Center; William Harvey, MD, IU Health Physicians Advanced Heart & Lung Clinic; Paul Hassoun, MD, Johns Hopkins University, Pulmonary and Critical Care Medicine; Nicholas Hill, MD, Tufts Medical Center; Lawrence Ho, MD, University of Washington Medical Center; Ahmed El-Bershawi, MD, Heba Ismail, MD, Pacific Pulmonary Medical Group; Behrouz Jafari, MD, VA Long Beach Healthcare System; Javier Jimenez, MD, South Miami Heart Specialists; Shilpa Johri,

MD, Pulmonary Associates of Richmond, Inc.; Christopher King, MD, Inova Fairfax Medical Campus; Tunay Kuru, MD, MedStar Georgetown University Hospital; Matthew Lammi, MD, Louisiana State University Health Sciences Center – New Orleans; Jennifer Davel, MD, Navneet Lather, MD, Community Heart and Vascular Facility of Community Hospital East; Deborah J. Levine, MD, University of Texas Health Science Center; Dustin R. Fraidenburg, MD, Roberto F. Machado, MD, University of Illinois at Chicago Hospital; Yolanda Mageto, MD, MPH, Baylor University Medical Center; Catherine J. Markin, MD, Legacy Medical Group - Pulmonary and Sleep Clinic; Scott E. Mattson, DO, Lutheran Medical Group; John W. McConnell, MD, Kentuckiana Pulmonary Associates; Colleen A. McEvoy, MD, Washington University; Boris I. Medarov, MD, Albany Medical College; Lana Melendres-Groves, MD, University of New Mexico; Jeffrey E. Michaelson, MD, Wellstar Medical Group - Pulmonary Medicine; Ruth Minkin, MD, New York Methodist Hospital; Hadi Chohan, MD, Syed I. Mobin, MD, Central Florida Pulmonary Group, PA; Sydney B. Montesi, MD, Massachusetts General Hospital; Majid Mughal, MD, McLaren Greater Lansing; Rachel E. Nisbet, MD, Hamilton Mill Clinical Research; Amy Olson, MD, National Jewish Health; Lavannya Pandit, MD, Michael E. DeBakey VA Medical Center; Joseph Parambil, MD, Cleveland Clinic; Bela Patel, MD, Memorial Hermann Hospital - Texas Medical Center; David Poch, MD, USCD Medical Center; Kenneth W. Presberg, MD, Medical College of Wisconsin/Froedtert Hospital; Michael A. Pritchett, DO, Pinehurst Medical Clinic; Jinesh Mehta, MD, Franck Rahaghi, MD, Cleveland Clinic Florida; Sudarshan Rajagopal, MD, PhD, Duke University Medical Center - Duke South Clinic; Amresh Raina, MD, Allegheny General Hospital; Gautam V. Ramani, MD, University of Maryland Medical Center Division of Cardiology; Abhijit Raval, MD, AnMed Health Pulmonary and Sleep Medicine; Ashwin K. Ravichandran, MD, St. Vincent Medical Group, Inc.; Ricardo Restrepo-Jaramillo, MD, University of South Florida; Michael Risbano, MD, UPMC Montfiore University Hospital; Franz Rischard, DO, University of Arizona; Justin Roberts, DO, Lancaster General Health; James Runo, MD, University of Wisconsin School of Medicine and Public Health; Shigeki Saito, MD, Tulane Medical Center; Jeffrey Sager, MD, Santa Barbara Cottage Hospital; Robert J Schilz, DO, PhD, University Hospitals Case Medical Center (UHCMC); Karim El-Kersh, MD, Jimmy Shaun Smith, DO, University of Louisville Physicians Outpatient Center; Shelley Shapiro, MD, PhD, Department of Veterans Affairs Greater Los Angeles Healthcare System; Kerri Akaya Smith, MD, Penn Medicine University City; Lewis Gilmer Satterwhite, MD, Leslie Spikes, MD, University of Kansas Medical Center; Irina Sobol, MD, New York Presbyterian - Weill Cornell Medicine; John Robert Spurzem, MD, University of Mississippi Medical Center; Joseph Stevenson, DO, Saint Mary's Regional Medical Center, Saint Mary's Health Network; John Swisher, PhD, MD, Statcare Pulmonary Consultants; Roxana Sulica, MD, ICAHN School of Medicine – Mount Sinai Beth Israel; Arunabh Talwar, MD, FCCP, Northwell Health; Nitin Y. Bhatt, MD, Rajive Tandon, MD, The Ohio State University Wexner Medical Center; James Tarver, MD, Florida Hospital; Thenappan Thenappan, MD, University of Minnesota; Austin B. Thompson III, MD, Nebraska Medicine; Fred Umeh, MD, Clinical Research Specialists, LLC; Rajat Walia, MD, St. Joseph's Hospital and Medical Center; Aaron B. Waxman, MD, PhD, Brigham and Women's Hospital; Sheila Weaver, DO, Temple

University Hospital, Temple Lung Center; Joel A. Wirth, MD, Chest Medicine Associates; Mark Yagan, MD, Saint Luke's Hospital of Kansas City; Peter Yau, MD, FCCP, Scott & White Memorial Hospital and Clinic; Mark Yoder, MD, Rush University Medical Center; Dianne L. Zwicke, MD, Aurora St. Luke's Medical Center.

INCREASE Steering Committee Members: Aaron Waxman, MD, PhD, Brigham and Women's Hospital; Victor Tapson, MD, Cedars Sinai; Steven D. Nathan, MD, Inova Fairfax Hospital

INCREASE Data Monitoring Committee: David Badesch, MD, FACP, FCCP, University of Colorado Denver; David Langleben, MD, Jewish General Hospital; Ronald Oudiz, MD, FACP, FACC, FCCP, UCLA Medical Center; Lisa Weisfeld, PhD, Statistics Collaborative

Independent Academic Statistician: Joseph Ibrahim, PhD, Gillings School of Global Public Health, University of North Carolina at Chapel Hill

2. Study Inclusion and Exclusion Criteria

2.1 Inclusion Criteria

1. Subject voluntarily gives informed consent to participate in the study.
2. Males and females aged 18 years or older at the time of informed consent.
   a. Females of reproductive potential[1] must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will:
      i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
      ii. Use 2 medically acceptable, highly effective forms of contraception[2] for the duration of the study, and at least 30 days after discontinuing study drug.
   b. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. The subject has a confirmed diagnosis of World Health Organization Group 3 pulmonary hypertension based on computed tomography imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomization. Subjects may have any form of interstitial lung disease or combined pulmonary fibrosis and emphysema.
4. Subjects are required to have a right heart catheterization within 1 year prior to randomization with the following documented parameters:
   a. Pulmonary vascular resistance >3 Wood Units and
   b. A pulmonary capillary wedge pressure of ≤15 mmHg and
   c. A mean pulmonary arterial pressure of ≥25 mmHg
5. Baseline 6-minute walk distance ≥ 100 meters.
6. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥30 days prior to randomization.
7. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.
8. Subjects with connective tissue disease must have a Baseline forced vital capacity of <70%.

[1] Females who are successfully sterilized (surgical sterilization methods include hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (defined as amenorrhea for at least 12 consecutive months) are not considered to be of reproductive potential.

[2] Medically acceptable, highly effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), and barrier methods (such as a condom or diaphragm) when used with a spermicide. For women of reproductive potential, a negative pregnancy test is required at Screening and Baseline prior to initiating study drug.

2.2 Exclusion Criteria

1. The subject has a diagnosis of pulmonary arterial hypertension or pulmonary hypertension for reasons other than World Health Organization Group 3 pulmonary hypertension due to interstitial lung disease as outlined in inclusion criterion 3.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any pulmonary arterial hypertension approved therapy including: prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, or soluble guanylate cyclase stimulator within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
   a. Pulmonary capillary wedge pressure >15 mmHg
   b. Left ventricular ejection fraction <40%.

Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) will not be excluded.

5. The subject is receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
6. Current use of any inhaled tobacco/marijuana products or significant history of drug abuse at the time of informed consent.
7. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization.
8. Initiation of pulmonary rehabilitation within 12 weeks prior to randomization.
9. In the opinion of the investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity) that would likely be the primary limit to ambulation (as opposed to pulmonary hypertension).
10. Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomization.
11. Severe concomitant illness limiting life expectancy (<6 months).
12. Acute pulmonary embolism within 90 days of randomization.

3. Methods

3.1 Procedure for 6-Minute Walk Test

The 6-minute walk test at peak plasma treprostinil exposure was conducted between 10 to 60 minutes after the most recent dose of study drug and the trough 6-minute walk test, at Week 15, was conducted at least 4 hours after the most recent study drug dose and at least 24 hours prior to the Week 16 6-minute walk test.

The 6-minute walk test was administered by the same tester at each study site throughout the study, whenever possible. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines[1,2] and the usual practice of the investigative site. Subjects receiving supplemental oxygen during the baseline 6-minute walk test continued to receive the same flow rate at all subsequent 6-minute walk test assessments.

The area used for the 6-minute walk test was pre-measured at approximately 30 meters in length and at least 2 to 3 m in width. There were no turns or significant curves to the 6-minute walk test area. The length was marked with gradations to ensure the accurate measurement of the distance walked. The area was well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods were allowed if the subject could no longer continue. If the subject needed to rest briefly, he/she could stand or sit and then begin again when he/she is sufficiently rested but the clock continued to run. At the end of 6 minutes, the tester called, “stop where you are” while simultaneously stopping the watch and then measured the distance walked.

Instructions to the Subject

Subjects were instructed that the preceding meal should be light. Subjects were told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test used the following exact dialogue with the subject:

> “The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say ‘STOP,’ please stand right where you are.”

After these instructions are given to the subject, the person administering the test then asked:

> “Do you have any questions about the test?”

The person administering the test then started the test by saying the following to the subject:

"Are you ready?"
"Start when I say 'GO.'"

The person administering the test told the subject the time at each minute by saying:

"You have 5 minutes to go."
"You have 4 minutes to go."
"You have 3 minutes to go."
"You have 2 minutes to go."
"You have 1 minute to go."

At 6 minutes, the person administering the test told the subject:

"Stop where you are."

No other instruction or encouragement were given during the test. Eye contact with the subject was to be avoided during the test.

4. Study Endpoints

PRIMARY ENDPOINT

- The primary endpoint is the change in 6-minute walk distance measured at peak exposure from Baseline to Week 16.

SECONDARY ENDPOINTS

- The secondary efficacy endpoints are (listed in hierarchical testing order):

1. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
2. Time to clinical worsening calculated as the time from randomization until 1 of the following criteria are met:
   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6-minute walk distance >15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
3. Change in peak 6-minute walk distance from Baseline to Week 12
4. Change in trough 6-minute walk distance from Baseline to Week 15

EXPLORATORY ENDPOINTS

- Exploratory endpoints are (not included in hierarchical testing):

1. Change in peak 6-minute walk distance from Baseline to Week 4
2. Change in peak 6-minute walk distance from Baseline to Week 8
3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Change in distance saturation product from Baseline to Week 16

Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They are specified in separate documents and are not covered in the statistical analysis plan.

SAFETY ENDPOINTS

- Safety endpoints are (not included in hierarchical testing):

1. Adverse events
2. Oxygenation as measured by pulse oximetry (saturation of peripheral capillary oxygenation) and supplemental oxygen requirement (L/min)
3. Pulmonary function tests, specifically: forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and lung diffusion capacity

4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms
7. Hospitalizations due to a cardiopulmonary indication
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

5. Statistical Methods

Primary End Point Analyses

MMRM methodology was used to assess treatment differences at Week 16 for change from baseline in peak6-minute walk distance. The model included the change from baseline at Week 16 as the dependent variable with treatment, week, and treatment by week interaction as fixed effects and baseline 6-minute walk distance as a covariate. This method allows for use of all available data in the analysis of longitudinal continuous outcomes; however, it assumes that the data are "missing at random" (MAR). That is, the probability that a value is missing depends only on the observed values and not the unobserved values. In some cases, this assumption is untenable, and the data are considered "missing not at random" (MNAR).

The assumption of MAR was examined by the sensitivity analyses using the control-based pattern-mixture model (PMM) method of Yuan (2014) and the approach of Permutt (2016), Mehrotra (2017) under MNAR.[3,4,5] If the results under MNAR differ from the results from the MMRM method, then the conclusion under the MAR assumption is questionable. In particular, (1) multiple imputation (MI) was done under control-based imputation and the MMRM analysis was carried out on the imputed data; and (2) tests of treatment effect were carried out over a range of plausible values for the treatment differences in a systematic manner.

The control-based PMM model creates imputed values for the active treatment group from the observed data in the placebo treatment group. This assumes that subjects who discontinue from active treatment would behave similarly after dropout to those in the placebo group. Treatment, baseline 6-minute walk distance, age at randomization, sex, and all observed values of the 6-minute walk were included in the multiple imputation model with 100 imputations, 200 burn-in imputations, and a noninformative prior. The results are shown below, which are similar with the results from the MMRM method

Estimated Treatment Difference (SE)	95% CI	p-value
24.69 (7.70)	9.59, 39.79	0.0014

The method of Permutt allows for a systematic and comprehensive exploration over the space of plausible assumptions and does not require imputation. The shift in change in 6MWD at Week 16 in the placebo group ranged from -60 meters to 0 meters and the shift in the active group ranged from -50 meters to -10 meters. These ranges were determined from a review of changes from baseline based on the pattern of missingness. The p-values for the test treatment effect were all significant ($p<0.033$) for all possible assumptions. Since the plausible range of deviations from MAR lies entirely within the range of statistical significance, the evidence for efficacy was convincing despite the missing data.

MI was designated as a sensitivity analysis for the MMRM. The imputed values were generated using the Markov chain Monte Carlo method assuming a multivariate normal distribution for the data. The Jeffreys prior with 100 imputations and 200 burn-in imputations was used. The ANCOVA model was fit to each set of imputed data and the results of the 100 estimates were combined under the Rubin (1987)

rule.[6] Note that MI generates imputed values under the MAR assumption. As discussed in the MMRM section above, there was no reason to discount the MAR assumption.

The protocol-specified analysis of the primary efficacy endpoint of change from baseline in peak 6-minute walk distance at Week 16 was analysis of covariance (ANCOVA). Change from baseline at Week 16 was the dependent variable with independent terms for baseline 6-minute walk distance and treatment in the ANCOVA model. Missing data were imputed as zero if the subject had died, was too ill to walk, or had experienced a clinical worsening event. For all other reasons, the last observation was carried forward. Since the assumptions for the ANCOVA were not met, a non-parametric ANCOVA was conducted under the single imputation rules above. Median treatment difference was estimated via the Hodges-Lehmann estimator. The conclusions of this analysis were concordant with the MMRM and MI analyses. This preplanned analysis has been deemed supplementary (Figure S6) in this manuscript due to the journal's policy with regards to missing data handling.

Secondary End Point Analyses

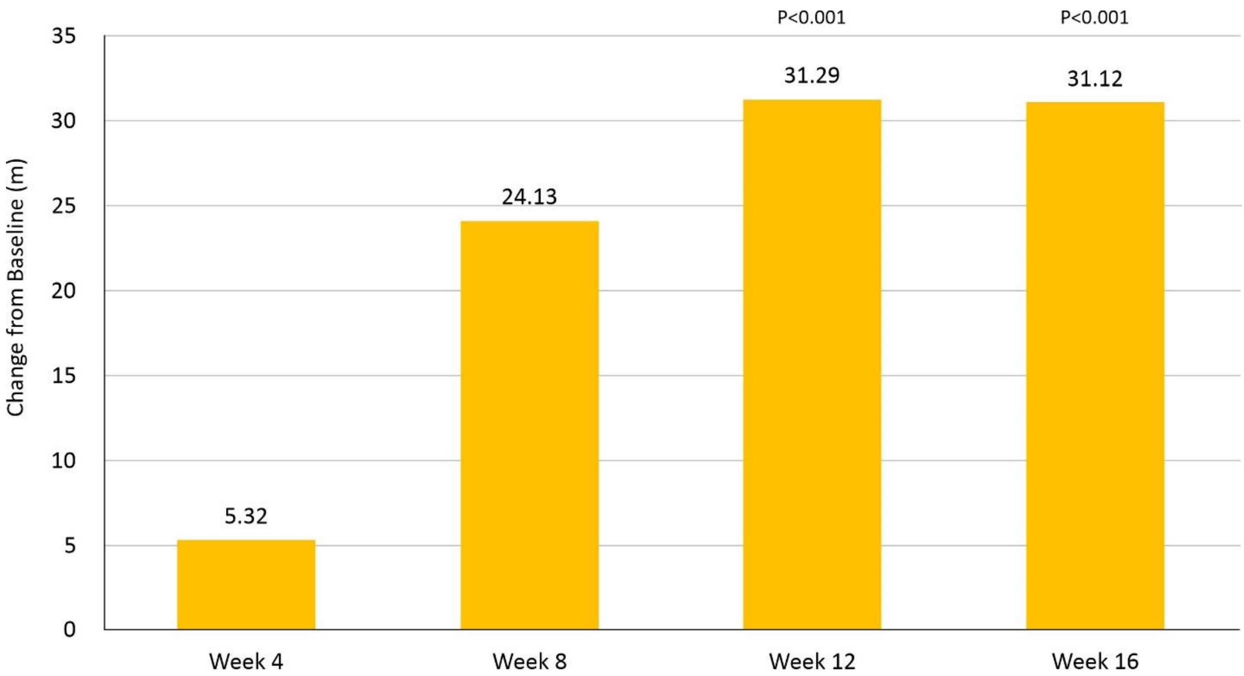
The NT-proBNP data were log-transformed prior to analysis due to non-normal distribution. Similar methods as described for the primary end point were applied to the NT-proBNP data.

Time to clinical worsening was assessed by calculation of the associated Kaplan-Meier estimates and the log-rank test stratified by baseline 6-minute walk distance. The hazard ratio was estimated from a Cox proportional hazards model that adjusted for baseline 6-minute walk distance.

The change in peak 6-minute walk distance at Week 12 was analyzed similarly to the primary end point. The change in 6-minute walk distance at Week 15 was analyzed via ANCOVA with missing data imputed using MI.

6. Supplementary Figures

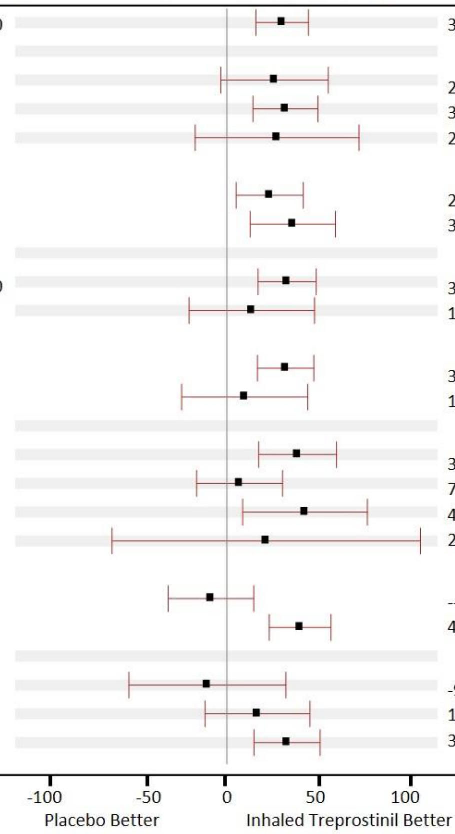
Figure S1. 6-Minute Walk Distance Treatment Effect Using Mixed Model Repeated Measurement Through Week 16.



A longitudinal data analysis using mixed model repeated measurement was also performed to estimate the treatment difference in change in peak 6-minute walk distance at Week 16. The mixed model repeated measurement includes the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment by week interaction as fixed effects; and baseline 6-minute walk distance as a covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors

Figure S2. Forest Plot on Subgroup Analyses of Peak 6-Minute Walk Distance (meter) at Week 16.

Subgroup	Inhaled Treprostinil # Patients	Placebo # Patients	LS Mean Difference (95% CI)
Overall	121	120	31.1 (16.9, 45.4)
Age Group			
<65 years	48	32	27.0 (-2.2, 56.1)
65 to 80 years	63	78	32.9 (15.2, 50.5)
≥80 years	10	10	28.3 (-16.2, 72.9)
Sex			
Male	55	68	24.3 (6.1, 42.5)
Female	66	52	36.9 (13.7, 60.0)
Baseline 6MWD Category			
≤350 meters	99	100	33.8 (18.0, 49.6)
>350 meters	22	20	14.6 (-19.5, 48.7)
Baseline DLCO (% Predicted)			
<40%	90	98	33.0 (17.7, 48.3)
≥40%	23	18	10.7 (-23.5, 45.0)
PH-ILD Etiology			
Idiopathic Interstitial Pneumonia	48	62	39.5 (18.3, 60.7)
Combined Pulmonary Fibrosis and Emphysema	30	28	7.9 (-15.4, 31.3)
Connective Tissue Disease	34	24	43.5 (9.6, 77.4)
Other	9	6	22.4 (-61.4, 106.3)
Baseline PVR Category			
<4 Wood units	27	25	--7.6 (-30.9, 15.6)
≥4 Wood units	94	95	40.8 (24.1, 57.6)
Maximum Study Drug Dose			
4-6 breaths	6	2	-9.5 (-52.2, 33.1)
7-9 breaths	37	24	17.7 (-10.9, 46.2)
10-12 breaths	77	92	33.7 (15.8, 51.7)
>12 breaths	1	2	

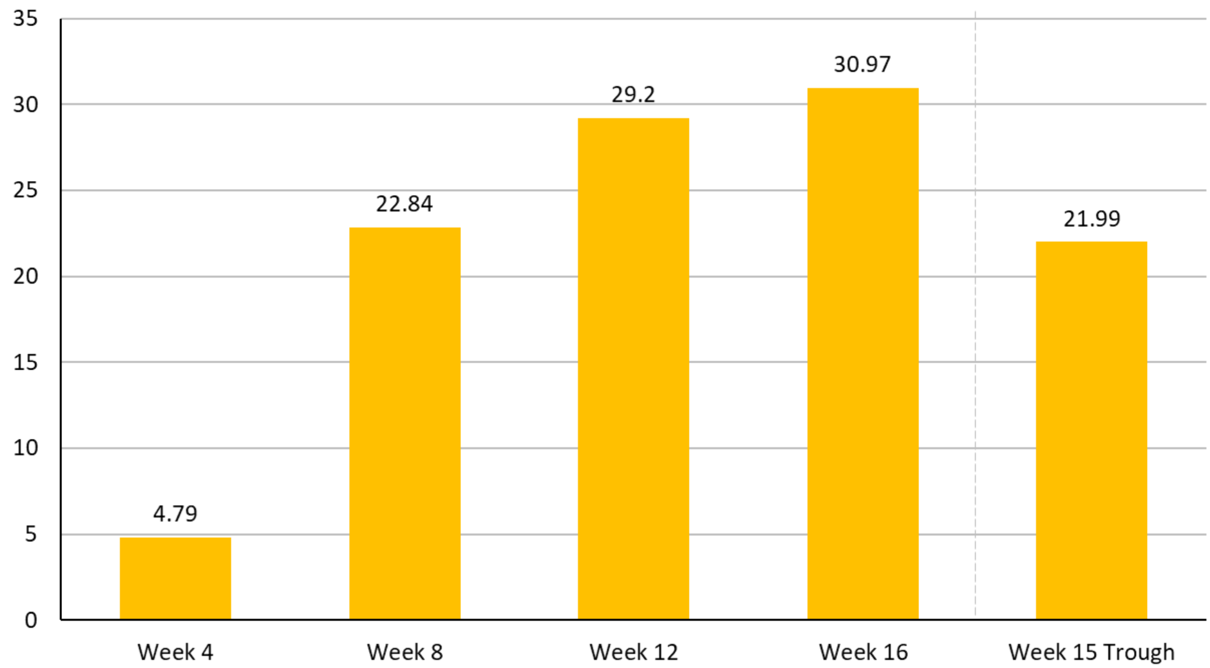


6MWD, 6-minute walk distance; CI, confidence interval; ILD, interstitial lung disease; PH, pulmonary hypertension; PVR, pulmonary vascular resistance

LS mean differences and their 95% confidence intervals, and p-values are from the mixed model repeated measures. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

For etiology, the “other” category includes chronic hypersensitivity pneumonitis and occupational lung disease.

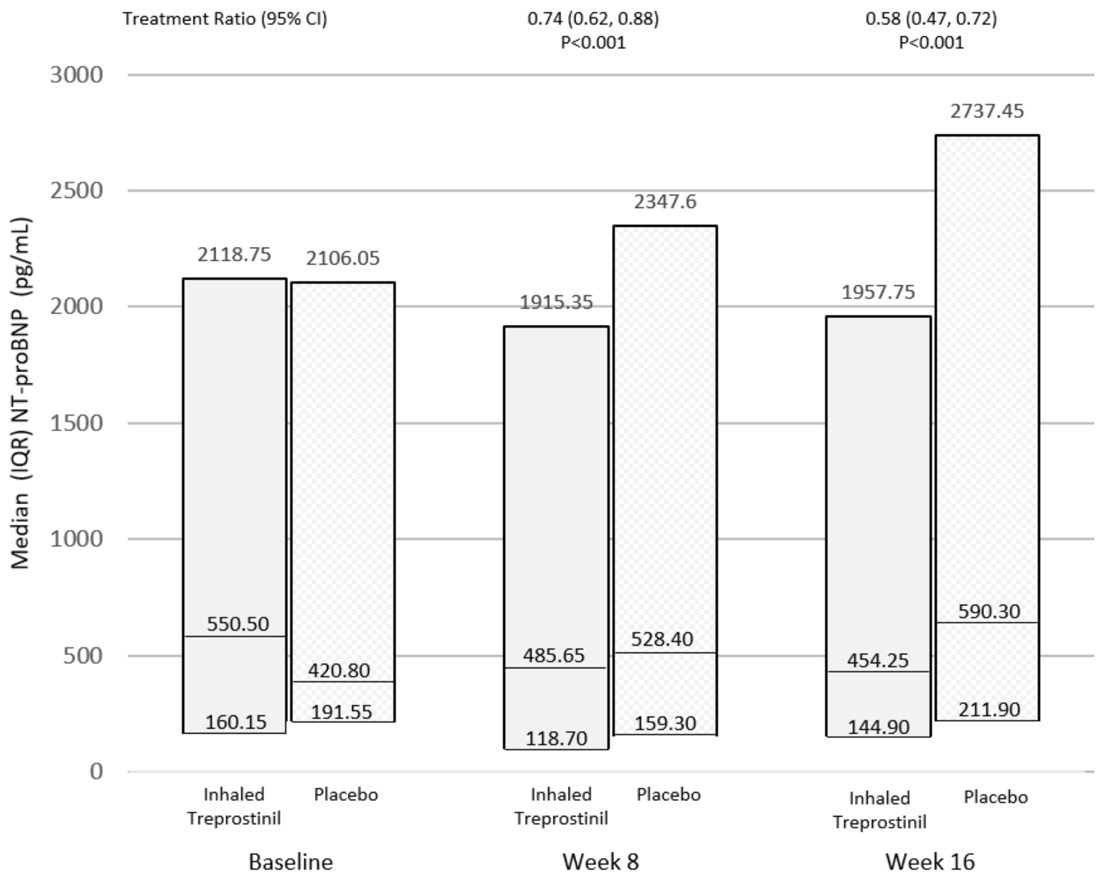
Figure S3. 6-Minute Walk Distance Treatment Effect Using Multiple Imputation Through Week 16.



Multiple imputation approach using a multivariate normal imputation model with the Markov Chain Monte Carlo method.

P-values are obtained from 100 multiple imputations using Markov Chain Monte Carlo estimation with ANCOVA model with change from Baseline in 6-minute walk distance as the dependent variable, treatment as fixed effect, and Baseline 6-minute walk distance measurement as a covariate.

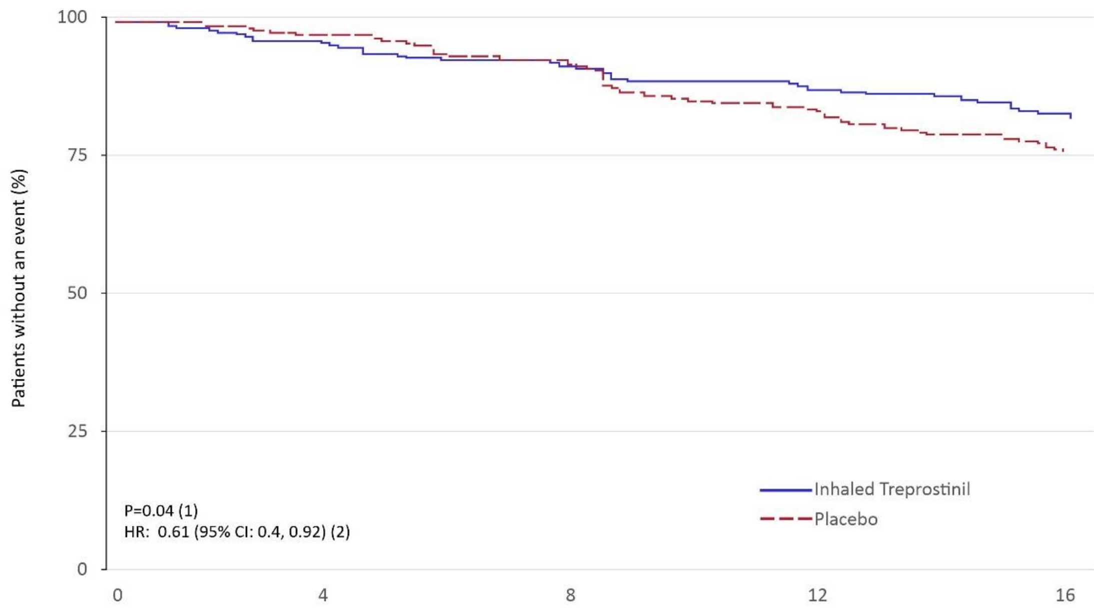
Figure S4. NT-proBNP Results by Study Visit (pg/mL).



CI, confidence interval; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide

As displayed above, inhaled treprostinil was associated with a 42% reduction in NT-proBNP compared to placebo at Week 16 (Treatment Ratio 0.58; 95% CI: 0.47, 0.72; P<0.001). Only subjects with a Baseline NT-proBNP measurement are included in this analysis. P-values, estimated treatment ratio, and associated 95% CIs (LS Mean difference expressed as ratio) are obtained from the analysis of covariance with change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Figure S5. Kaplan-Meier Plot of Time to First Clinical Worsening Event.



# Patients at each timepoint	0	4	8	12	16
Inhaled Treprostinil	163	151	138	127	93
Placebo	163	152	136	116	87

CI, confidence interval; HR, hazard ratio

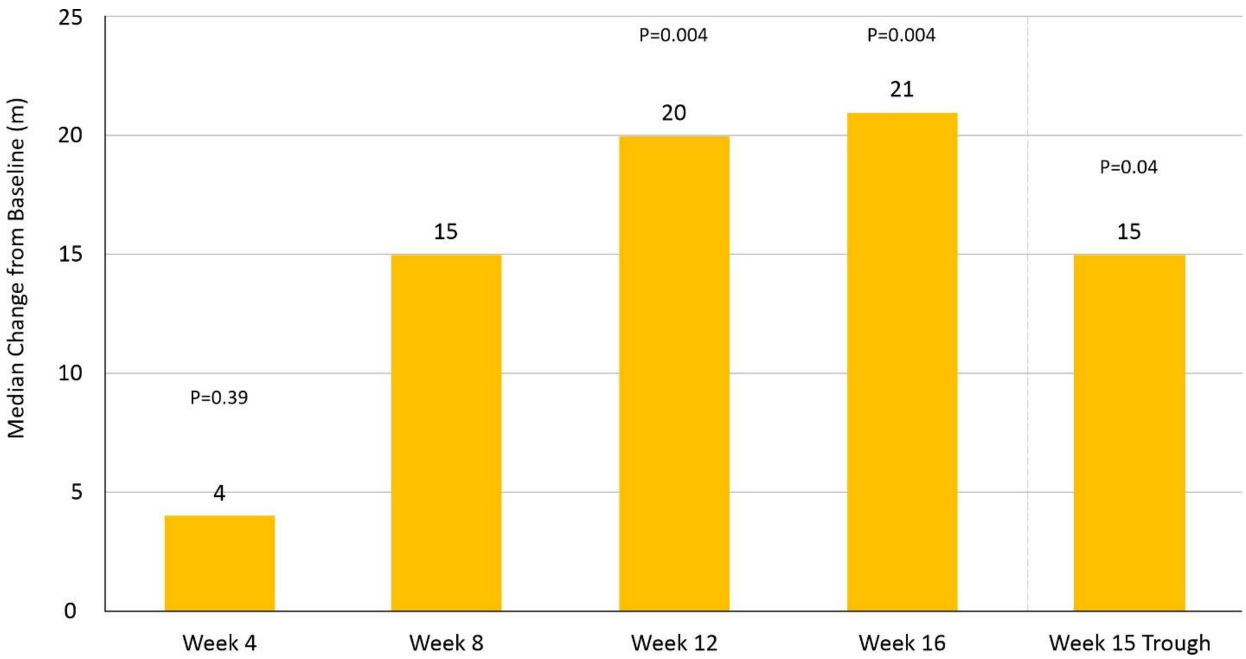
Subjects who discontinued from the study early had their time to first clinical worsening event censored at their last visit. Subjects who did not experience a clinical worsening event had their time to first clinical worsening event censored at the study termination date.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

(1) P-value was calculated with log-rank test stratified by baseline 6-minute walk distance category.

(2) Hazard ratio, 95% CI, and p-value were calculated with proportional hazards model with treatment and baseline 6-minute walk distance (continuous) as explanatory variables.

Figure S6. Hodges-Lehmann Estimate of Treatment Effect for 6-Minute Walk Distance Through Week 16.



For those subjects who withdrew early due to death, were too ill to walk, or had no 6-minute walk distance measurement due to a clinical worsening event, the 6-minute walk distance was set to 0; for all other withdrawals without a measurement, last observation carried forward was used for imputation.

P-values are obtained from nonparametric ANCOVA adjusted for Baseline 6-minute walk distance category.

7. Supplementary Tables

Table S1. Summary of Screen Failure Reasons.

Screen Failure Reason Reported	N=136*
• Did not meet inclusion criteria per right heart catheterization parameters	58
• Consent withdrawn/decided not to continue	14
• Did not have qualifying computed tomography scan	12
• Baseline 6-minute walk test <100 m	12
• Exacerbation of underlying lung disease/active upper respiratory infection within 30 days prior to randomization	11
• Connective tissue disease patient did not have Baseline FVC <70%	11
• Receiving other pulmonary arterial hypertension therapy	6
• Subject has a diagnosis of pulmonary hypertension other than Group 3	5
• In the opinion of the Investigator, the subject had any condition that would interfere with the interpretation of study assessments or meeting protocol requirements, including attending all study visits	6
• Subject not on stabilized dose of background medication for at least 30 days prior to randomization	4
• Pulmonary rehabilitation initiated within 12 weeks prior to randomization	3
• Hospitalization prior to randomization	2
• Receiving greater than 10L/min of O_2 at rest at Baseline	2
• Current use of any inhaled tobacco/marijuana products or significant history of drug abuse	1
• Did not meet age/agree to birth control requirement	1
• Severe concomitant illness limiting life expectancy (< 6 months)	1
• Subject passed away while in screening window	1

FVC, forced vital capacity

*Note, 10 patients had 2 reasons and 1 patient had 5 reasons for screen failure reported.

Table S2. Additional Baseline Patient Characteristics.

	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
6-minute walk distance, meters; mean (range)	254.1 (100-538)	265.1 (30-505)	259.6 (30-538)
Median	256.0	260.0	259.0
Pulmonary vascular resistance, Woods units; mean (range)	6.369 (3.11-18.05)	6.013 (3.06-17.62)	6.191 (3.06-18.05)
Median	5.570	5.060	5.275
NT-proBNP, pg/mL; mean (range)	1857.53 (10.2-21942.0)	1808.86 (23.0-16297.0)	1832.88 (10.2-21942.0)
Median*	550.50	420.80	503.85
Pulmonary arterial pressure, mmHg; mean (range)	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
Pulmonary capillary wedge pressure, mmHg; mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV_1 % Predicted; mean (range)	63.9 (23, 120)	65.0 (22, 145)	
Median	63.0	63.0	
FVC % Predicted; mean (range)	62.5 (24, 130)	63.8 (20, 134)	
Median	60.0	61.0	
TLC % Predicted; mean (range)	62.9 (25, 126)	64.2 (30, 109)	
Median	62.0	62.5	
DLCO % Predicted; mean (range)	30.0 (5, 86)	28.1 (1, 86)	
Median	29.0	26.0	

DLCO, lung diffusion capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; TLC, total lung capacity

*N=156 inhaled treprostinil; N=160 placebo.

Table S3. St. George's Respiratory Questionnaire Results.

The St. George's Respiratory Questionnaire has a range of results from 0 to 100, with higher scores indicating greater impairment and with a minimum clinically important difference of 4 points.

	Inhaled Treprostinil N=163		Placebo N=163	
Visit / Statistic	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**
Baseline				
n	143		134	
Mean (SD)	57.17 (15.77)		57.67 (15.78)	
Median	59.80		56.30	
Interquartile	45.60, 67.90		46.50, 70.70	
Min, Max	14.7, 94.9		18.4, 88.6	
Week 16				
n	143	143	134	134
Mean (SD)	55.91 (17.07)	-1.25 (10.99)	57.49 (15.33)	-0.18 (10.72)
Median	56.30	-0.70	55.50	0.10
Interquartile	40.50, 67.00	-7.10, 5.20	46.80, 69.70	-6.50, 6.10
Min, Max	3.5, 92.0	-40.4, 29.0	16.9, 96.5	-31.9, 33.3
LS Mean (SE)		-1.30 (0.87)		-0.13 (0.90)
LS Mean Difference (SE) and (95% CI)	-1.18 (1.25) (-3.63, 1.28)			

ANCOVA, analysis of covariance; CI, confidence interval; LS Mean, least squares mean; SD, standard deviation; SE, standard error

The changes from baseline in Total Score and each of the 3 domain scores were analyzed by parametric ANCOVA with no imputation for missing data.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Table S4. Distance Saturation Product Results by Study Visit (m%).

Visit / Variable Statistic	Inhaled Treprostinil N=163	Placebo N=163
Baseline		
n	118	109
Mean (SD)	208.140 (81.130)	218.247 (77.405)
Median	201.320	215.760
Interquartile	150.060, 256.750	170.800, 268.800
Min, Max	77.04, 421.07	63.00, 417.35
Week 16 Change from Baseline		
n	118	109
Mean (SD)	7.607 (45.680)	-4.803 (53.026)
Median	8.385	-1.950
Interquartile	-12.960, 34.890	-38.180, 32.000
Min, Max	-217.26, 117.42	-184.85, 129.28
LS Mean (SE)	7.2 (4.5)	-4.3 (4.7)
LS Mean Difference (SE) and 95% CI	11.51 (6.5), 95% CI (-1.33, 24.35)	

ANCOVA, analysis of covariance; CI, confidence interval; LS Mean, least squares mean; SD, standard deviation; SE, standard error; SpO2, saturation of peripheral capillary oxygenation

Change in distance saturation product is the product of distance walked and lowest SpO2 recorded during the 6-minute walk test.[7] Change from baseline to Week 16 in distance saturation product was analyzed by parametric ANCOVA with no imputation for missing distance saturation product values.

The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Table S5. Serious Adverse Events by Preferred Term

Serious Adverse Events	Inhaled treprostinil N=163 n	Placebo N=163 n
Any Serious Event	53 events in 38 patients (23.3%)	89 events in 42 patients (25.8%)
Acute respiratory failure	4	5
Death with unknown cause	3	1
Dyspnoea	3	7
Interstitial lung disease	3	2
Bronchitis	2	1
Chronic obstructive pulmonary disease	2	2
Chronic respiratory failure	2	0
Respiratory failure	2	5
Upper respiratory tract infection	2	1
Acute myocardial infarction	1	2
Acute right ventricular failure	1	0
Arrhythmia	1	0
B-cell lymphoma	1	0
Bronchopulmonary aspergillosis	1	0
Cardiac arrest	1	2
Cardiac failure congestive	1	2
Cardiopulmonary failure	1	0
Cellulitis	1	0
Cerebral haemorrhage	1	0
Chest pain	1	1
Combined pulmonary fibrosis and emphysema	1	0
Cor pulmonale	1	0
Haemoptysis	1	0
Hyperglycaemia	1	0
Hypervolaemia	1	0
Hypoxia	1	0
Idiopathic pulmonary fibrosis	1	4
Influenza	1	1
Left ventricular failure	1	0
Pain in extremity	1	0
Pneumonia	1	9
Pneumothorax	1	1
Pulmonary hypertension	1	1
Pulmonary oedema	1	0
Rhinovirus infection	1	0
Right ventricular failure	1	2
Syncope	1	1
Tachycardia	1	0
Abdominal pain	0	2
Acute kidney injury	0	1
Aspiration	0	1
Atrial fibrillation	0	1
Bradycardia	0	1
Cardiac failure	0	2
Cardiac failure acute	0	1
Cardiogenic shock	0	1
Chronic right ventricular failure	0	1
Coagulopathy	0	1
Cor pulmonale acute	0	1
Coronary artery disease	0	1
Disease progression	0	2
Epistaxis	0	1

Fluid overload	0	4
Haematochezia	0	1
Hypertension	0	1
Lumbar vertebral fracture	0	1
Metabolic encephalopathy	0	1
Pain	0	1
Pneumonia influenzal	0	1
Post procedural infection	0	1
Presyncope	0	2
Pulmonary congestion	0	1
Respiratory distress	0	1
Scleroderma	0	1
Sepsis	0	2
Transplant dysfunction	0	1
Urosepsis	0	1

Table S6. Analysis of Lung Function Test Parameters Using Mixed Model Repeated Measurement.

Variable Visit Treatment	N	LS Mean	Contrast: Inhaled treprostinil - Placebo Estimated Difference (95% CI)	P-value
FVC (mL)				
Week 8				
Inhaled treprostinil	142	5.49	28.47	
Placebo	141	-22.98	(-30.81, 87.74)	0.35
Week 16				
Inhaled treprostinil	130	9.77	44.40	
Placebo	126	-34.63	(-25.25, 114.05)	0.21
FVC (% predicted)				
Week 8				
Inhaled treprostinil	142	0.77	1.79	
Placebo	141	-1.02	(0.37, 3.21)	0.01
Week 16				
Inhaled treprostinil	130	1.07	1.80	
Placebo	126	-0.72	(0.20, 3.39)	0.03
FEV_1 (mL)				
Week 8				
Inhaled treprostinil	142	-21.34	-8.95	
Placebo	141	-12.39	(-57.16, 39.26)	0.72
Week 16				
Inhaled treprostinil	130	-32.18	-2.56	
Placebo	126	-29.62	(-57.67, 52.55)	0.93
FEV_1 (% predicted)				
Week 8				
Inhaled treprostinil	142	-0.18	0.57	
Placebo	141	-0.75	(-0.83, 1.96)	0.43
Week 16				
Inhaled treprostinil	130	-0.24	0.38	
Placebo	126	-0.62	(-1.25, 2.01)	0.65
TLC (mL)				
Week 8				
Inhaled treprostinil	135	-38.75	-16.23	
Placebo	136	-22.51	(-141.9, 109.41)	0.80
Week 16				
Inhaled treprostinil	127	45.43	17.37	
Placebo	116	28.06	(-158.9, 193.61)	0.85
TLC (% predicted)				
Week 8				
Inhaled treprostinil	135	-0.05	0.28	
Placebo	136	-0.32	(-1.49, 2.05)	0.76
Week 16				
Inhaled treprostinil	127	2.52	1.49	
Placebo	116	1.03	(-1.57, 4.54)	0.34

DLCO (mL/min/mmHg)				
Week 8				
Inhaled treprostinil	136	-0.27	0.19	
Placebo	136	-0.47	(-0.45, 0.84)	0.56
Week 16				
Inhaled treprostinil	128	-0.61	0.02	
Placebo	112	-0.63	(-0.73, 0.76)	0.96
DLCO (% predicted)				
Week 8				
Inhaled treprostinil	136	-0.13	1.07	
Placebo	136	-1.20	(-0.32, 2.47)	0.13
Week 16				
Inhaled treprostinil	128	-1.14	0.60	
Placebo	112	-1.74	(-0.93, 2.14)	0.44

CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity;; LS Mean, least squares mean; SE, standard error; TLC, total lung capacity

LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in pulmonary function test parameter as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline measurement as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

The confidence intervals and p-values have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Table S7. SpO_2 (%) Measured by Pulse Oximetry Results at Baseline and Week 16.

	Inhaled Treprostinil N=163		Placebo N=163		
Visit Statistic	**Value**	**Change from Pre-walk**	**Value**	**Change from Pre-Walk**	**P-value***
Baseline Pre-walk SpO_2 (%)					
n	163		162		
Mean (SD)	95.3 (3.95)		94.5 (4.81)		
Median	96.0		96.0		
Min, Max	72, 100		68, 100		
Baseline During Walk SpO_2 (%)					
n	154	154	153	153	0.13
Mean (SD)	80.3 (8.22)	-15.0 (7.87)	78.5 (8.20)	-16.1 (7.76)	
Median	81.0	-14.0	78.0	-15.0	
Min, Max	53, 99	-41, 2	53, 98	-39, 4	
Baseline Post-walk SpO_2 (%)					
n	163	163	162	162	0.17
Mean (SD)	85.3 (7.31)	-9.9 (6.50)	83.7 (8.74)	-10.9 (8.06)	
Median	86.0	-10.0	83.5	-11.0	
Min, Max	59, 100	-26, 5	57, 99	-39, 7	
Week 16 Pre-walk SpO_2 (%)					
n	130		122		
Mean (SD)	94.5 (4.35)		94.5 (4.22)		
Median	95.0		95.0		
Min, Max	74, 100		78, 100		
Week 16 During Walk SpO_2 (%)					
n	123	123	114	114	
Mean (SD)	76.8 (7.70)	-17.6 (7.01)	78.2 (9.28)	-16.6 (9.04)	0.27
Median	77.0	-17.0	79.0	-16.0	
Min, Max	46, 99	-38, -1	28, 98	-61, -1	
Week 16 Post-walk SpO_2 (%)					
n	128	128	122	122	0.07
Mean (SD)	82.1 (9.24)	-12.4 (8.05)	83.7 (7.75)	-10.8 (7.09)	
Median	83.0	-13.0	84.0	-11.5	
Min, Max	51, 100	-29, 3	65, 100	-31, 6	

SD, standard deviation; SpO_2, saturation of peripheral capillary oxygenation

*P-values are calculated from analysis of covariance with change from pre-walk as dependent variable, treatment as fixed effect, and baseline SpO2 as covariate.

Table S8. Supplemental Oxygen Use (L/min) at Baseline and Week 16.

	Inhaled Treprostinil N=163		Placebo N=163		
Visit Statistic	**Value**	**Change from Baseline**	**Value**	**Change from Baseline**	**P-value***
Baseline Pre-walk (L/min)					
n	163		163		
Mean (SD)	2.7 (2.2)		2.4 (2.0)		
Median	3.0		2.0		
Min, Max	0, 10		0, 8		
Baseline During Walk (L/min)					
n	163		163		
Mean (SD)	4.9 (4.0)		4.5 (3.8)		
Median	4.0		4.0		
Min, Max	0, 25		0, 15		
Week 16 Pre-walk (L/min)					
n	131	131	129	129	0.18
Mean (SD)	3.0 (2.5)	0.4 (1.4)	2.9 (2.4)	0.6 (1.3)	
Median	3.0	0.0	3.0	0.0	
Min, Max	0, 10	-3, 6	0, 10	-3, 5	
Week 16 During Walk (L/min)					
n	129	129	123	123	0.39
Mean (SD)	4.9 (4.0)	0.1 (0.8)	4.6 (3.7)	0.1 (0.3)	
Median	4.0	0.0	4.0	0.0	
Min, Max	0, 25	-2, 8	0, 15	0, 3	

SD, standard deviation

Subjects who did not use supplemental oxygen were coded as 0 in the summaries.

Subjects who received supplemental oxygen during the Baseline 6-minute walk test continued to receive the same flow rate at all subsequent 6-minute walk test assessments.

*P-values are calculated from analysis of covariance with change from baseline as dependent variable, treatment as fixed effect, and baseline oxygen use as covariate.

8. References

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EXHIBIT 24

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med 2021;384:325-34. DOI: 10.1056/NEJMoa2008470

This supplement containing the following items:

- Original Protocol, 21Oct2015 (Link)
- Final Protocol, Amendment 3, 15Feb2017 (Link)
- Study Protocol Summary of Changes document (Link)
  - Amendment 1, 20Nov2015
  - Amendment 2, 13Sept2016
  - Amendment 3, 15Feb2017
- Original Statistical Analysis Plan, 27Feb2019 (Link)
- Final Statistical Analysis Plan, Amendment 1, 12Dec2019 (Link)
- Statistical Analysis Plan Summary of Changes document (Link)

Original Protocol - RIN-PH-201

21October 2015

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

IND 70,362

Protocol RIN-PH-201

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date: 21 October 2015

LIST OF CONTACTS FOR STUDY

Study Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709
	[redacted]
	[redacted]
	[redacted]
	[redacted]
[redacted]	[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease," dated 21 October 2015 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56 and 312 and any local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of United Therapeutics Corp.

I also have read the current Clinical Investigators' Brochure for inhaled treprostinil and acknowledge that review of the information contained in the Clinical Investigators' Brochure is a requirement for Investigators before using inhaled treprostinil in a clinical trial.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and Ethics Committee / Institutional Review Board approval documents have been obtained.

______________________________ ______________________________
Signature of Principal Investigator Date

______________________________ ______________________________
Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease
Study Phase	Phase II/III
Indication	Pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE)
Primary Objective	To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE
Primary Endpoint	To evaluate the change in six-minute walk distance (6MWD) measured at peak exposure from Baseline to Week 16
Secondary Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD from Baseline to Week 12 2. Change in plasma concentration of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) from Baseline to Week 16 3. Change in trough 6MWD from Baseline to Week 15
Exploratory Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD at Week 4 2. Change in peak 6MWD at Week 8 3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16 4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met: a. Hospitalization due to a cardiopulmonary indication

	b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart c. Death (all causes) d. Lung transplantation 5. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16 6. Change in distance saturation product (DSP) from Baseline to Week 16
Safety Endpoints	1. Adverse events (AEs) 2. Oxygenation a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2]) b. Supplemental oxygen requirement (L/min) 3. Pulmonary function: a. Forced expiratory volume in one second (FEV_1) b. Forced vital capacity (FVC) c. Total lung capacity (TLC) d. Lung diffusion capacity (DLCO) 4. Clinical laboratory parameters 5. Vital signs 6. Electrocardiograms (ECG) 7. Hospitalization due to a cardiopulmonary indication 8. Exacerbations of underlying lung disease; defined as worsening of respiratory symptoms which require the modification or addition of systemic corticosteroids, antibiotics, or both
Study Design	Multi-center, randomized, double-blinded, placebo-controlled, 16-week, parallel group study
Sample Size	Approximately 314 subjects at approximately 75 centers
Summary of Subject Eligibility Criteria	Inclusion criteria: 1. Subject voluntarily gives informed consent to participate in the study.

2. Males and females aged 18 – 79 years at the time of informed consent.
   a. Females of reproductive potential must be non-pregnant (as confirmed by a serum pregnancy test at screening) and non-lactating, and will:
      i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
      ii. Use two medically acceptable, highly-effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug.
   b. Males must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. The subject has a confirmed diagnosis (based on computed tomography [CT] imaging and pulmonary function tests [PFTs] performed within six months prior to the first dose of study drug) of World Health Organization (WHO) Group 3 PH associated with one of the following:
   a. Idiopathic interstitial pneumonia (IIP) including:
      i. Idiopathic pulmonary fibrosis (IPF)
      ii. Idiopathic nonspecific interstitial pneumonia
      iii. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
      iv. Desquamative interstitial pneumonia (DIP)
      v. Cryptogenic organizing pneumonia (COP)
      vi. Acute interstitial pneumonitis (AIP)
      vii. Idiopathic lymphoid interstitial pneumonia
      viii. Idiopathic pleuroparenchymal fibroelastosis

ix. Unclassifiable idiopathic interstitial pneumonia

b. Chronic hypersensitivity pneumonitis (CHP)

c. Occupational lung disease (drug or radiation-induced)

d. Combined pulmonary fibrosis and emphysema (CPFE)

4. Subjects are required to have a right heart catheterization (RHC) within one year prior to the first dose of study drug with the following documented parameters:
   a. Pulmonary vascular resistance (PVR) $\geq$ 4 Wood Units (WU) and
   b. A left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) of $\leq$ 12 mmHg if PVR $\geq$ 4 WU to < 6.25 WU or $\leq$ 15 mmHg if PVR $\geq$ 6.25 WU and
   c. A mean pulmonary arterial pressure (mPAP) of $\geq$ 30 mmHg

Note: For subjects receiving background therapy with an FDA approved medication (i.e., endothelin receptor antagonist [ERA], phosphodiesterase type-5 inhibitor [PDE-5I], or soluble guanylate cyclase stimulator [sGC]) for pulmonary arterial hypertension (PAH), the RHC must be performed after the initiation of aforementioned PAH therapy to ensure the subject meets the required RHC parameters.

5. An uncorrected diffusing capacity of the lungs for carbon monoxide (DLCO) of < 50%

6. Baseline 6MWD $\geq$ 100 meters

7. The subject is either not receiving any PAH-approved oral therapy (ERA, PDE-5I, or sGC), or is receiving monotherapy (ERA, PDE-5I, or sGC) for at least 90 days and receiving a stable dose for $\geq$ 30 days prior to randomization.

8. Subjects on a chronic medication for underlying lung disease must be on a stable and optimized dose for $\geq$ 30 days prior to the first dose of study drug. Subjects receiving pirfenidone or nintedanib must have been receiving treatment for at least

90 days and on a stable dose for at least 30 days prior to the first dose of study drug.

9. Subjects on a supportive medication therapy (*e.g.,* anticoagulants, diuretics, oxygen, etc.) must be on a stable and optimized dose for $\geq$ 30 days prior to the first dose of study drug. Exceptions are the discontinuation or dose changes of anticoagulants and / or dose change of diuretics.
10. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

Exclusion criteria:

1. The subject has a diagnosis of pulmonary arterial hypertension (PAH) or PH for reasons other than ILD as outlined in inclusion criterion 3. This would include, but is not limited to, the concomitant presence of thromboembolic disease (acute or chronic), untreated or inadequately treated obstructive sleep apnea (OSA), connective tissue disease (including but not limited to systemic sclerosis, scleroderma, or systemic lupus erythematosus [SLE]), sarcoidosis, human immunodeficiency virus (HIV)-1 infection, toxin exposure such as methamphetamine or anorexigen use, and other conditions of the WHO Group I, II, IV, and V classification.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any prostacyclin therapy (i.e., epoprostenol, treprostinil, iloprost, or beraprost) within 30 days of informed consent, except for acute vasoreactivity testing.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
    a. LVEDP or PCWP > 15 mmHg (or > 12 mmHg if PVR $\geq$ 4 to < 6.25 WU)

b. Left ventricular ejection fraction < 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography.

Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) will not be excluded.

5. Subjects must not have three or more of the following left ventricular disease/dysfunction risk factors:
   a. Body Mass Index (BMI) ≥ 30 kg/m^2
   b. History of Essential Hypertension
   c. Diabetes Mellitus – any type
   d. Historical evidence of significant coronary disease established by any one of the following:
      i. history of myocardial infarction or percutaneous coronary intervention or angiographic, or
      ii. evidence of coronary artery disease (> 50% stenosis in at least one coronary artery), or
      iii. positive stress test with imaging, or previous coronary artery bypass graft, or stable angina
6. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
7. Use of any inhaled tobacco products or significant history of drug abuse within six months prior to first dose of study drug.
8. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of the first dose of study drug.
9. Initiation of pulmonary rehabilitation within 12 weeks prior to the first dose of study drug.
10. The subject has uncontrolled systemic hypertension as evidenced by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.

	11. The subject has any form of congenital heart disease or congenital heart defect (repaired or unrepaired) (other than a patent foramen ovale [PFO]). 12. The subject has anemia as defined by a screening hemoglobin value < 9.0 g/dL, active infection, or any other condition that would interfere with the interpretation of study assessments. 13. The subject has a Body Mass Index $\geq$ 40 kg/m^2. 14. The subject has any musculoskeletal disorder (*i.e.,* arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (*i.e.,* cane or walker), or has any other condition that would limit ambulation. 15. Use of any investigational drug/device, or participation in any investigational study within 30 days prior to the first dose of study drug.
Drug Dosage and Formulation	Inhaled treprostinil (6 mcg/breath) or placebo Treatment phase: All subjects will initiate inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) four times daily (during waking hours). Study drug doses should be maximized throughout the study, dose escalations (additional one breath four times daily) can occur up to every three days with a target dosing regimen of 9 breaths (54 mcg) four times daily and a maximum dose of up to 12 breaths (72 mcg) four times daily, as clinically tolerated.
Control Group	Placebo
Route of Administration	Inhaled
Procedures	Subjects will be assessed during Screening and Baseline to determine eligibility for the study. Once eligible, five Treatment Phase visits to the clinic will be required at Weeks 4, Week 8, Week 12, Week 15, and Week 16 (Final study visit). An early termination (ET) visit will be conducted for subjects who end treatment prior to Week 16; all assessments planned for the final Week 16 visit will be conducted during the ET visit, as applicable. Subjects will

	also be contacted at least weekly by telephone or email to assess tolerance to study drug, AEs, and changes to concomitant medications. Key Assessments: • Pregnancy test: Females of childbearing potential will undergo a serum pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit. • Blood for NT-Pro-BNP and clinical labs will be obtained at Baseline, Week 8, and Week 16. • A peak 6MWT will be conducted at Baseline, Week 4, Week 8, Week 12, and Week 16/ET. • A trough 6MWT will be performed at Week 15 (at least 24 hours prior to the Week 16/ET visit). • Pulse oximetry will be performed immediately prior to, during, and immediately after each 6MWT. • PFTs will be conducted at Baseline, Week 8, and Week 16/ET. • SGRQ will be completed at Baseline and Week 16/ET. • An optional blood sample will be collected for the analysis of biomarkers (specific targets to be determined) at Baseline and Week 16/ET. • An ECG will be conducted at Baseline and Week 16/ET. • Time to clinical worsening, hospitalizations due to cardiopulmonary indications, and exacerbations of underlying lung disease will be evaluated from the time of informed consent until study discontinuation.
Statistical Considerations	Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (two-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD measured at peak exposure assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%. The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. The

	clinical hypothesis is that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between two treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.
Sponsor	United Therapeutics Corp. 55 T.W. Alexander Dr. P.O. Box 14186 Research Triangle Park, NC 27709 United States of America

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1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary hypertension (PH) is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance. The World Health Organization (WHO) classifies PH due to lung diseases and/or hypoxemia as WHO Group 3 PH (Simonneau 2009). This classification includes PH due to interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).

Interstitial lung disease encompasses a heterogeneous group of parenchymal lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs within the lungs (Travis 2013, Seeger 2013). Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs. The symptomatology of ILD is non-specific, and covers a wide range of symptoms, whose severity can vary substantially among patients. The incidence of PH in ILD has been reported in up to 86% of patients and is associated with a poorer prognosis and decreased quality of life (Nathan 2008, Nathan 2013).

Combined pulmonary fibrosis and emphysema characterized by emphysema, fibrosis, and abnormalities of gas exchange (Jankowich 2012). Up to 50% of CPFE patients have been reported to develop PH with increased pulmonary vascular resistance (PVR) associated with a decreased survival (Cottin 2010; Seeger 2013).

There are no approved treatments for PH in patients with ILD or CPFE; however, the results of some approved therapies for pulmonary arterial hypertension (PAH) have stimulated further investigation in these indications (Seeger 2013, Saggar 2014, Agarwal 2015, Roccia 2013).

1.2 INHALED TREPROSTINIL BACKGROUND

1.2.1 General Pharmacology

Treprostinil, 2-[[(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid, is a chemically stable tricyclic analogue of prostacyclin. The pharmacology of treprostinil is well-characterized and approved for the treatment of PAH following either the subcutaneous (SC), intravenous (IV), inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

Prostacyclin is known to lower pulmonary artery pressure, increase cardiac output without affecting the heart rate, improve systemic oxygen transport and possibly reverse pulmonary arterial remodeling. There is increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells, along with vasodilation, may contribute to the therapeutic effects of prostacyclin in the treatment of PAH. Treprostinil acts by triggering direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. *In vitro*, treprostinil induced concentration dependent relaxation of rabbit isolated pre-contracted mesenteric arteries and inhibited adenosine diphosphate induced platelet aggregation in human and rat platelet rich plasma. In animals, the vasodilatory effects

of treprostinil reduce right and left ventricular afterload, thereby increasing cardiac output and stroke volume. The mechanism of action of treprostinil is therefore likely to be multifactorial.

Treprostinil for inhalation (Tyvaso®) is approved in the United States and Israel for the treatment of PAH (WHO Group I) in patients with New York Heart Association (NYHA) functional classification III symptoms, to increase exercise ability.

1.2.2 General Toxicology

A well-defined clinical safety profile exists for treprostinil sodium; acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies have been performed in both rats and dogs and support the chronic administration to patients (Remodulin® Package Insert 2014).

The toxicokinetic profile of treprostinil was also evaluated in acute and repeat dose toxicity studies of up to 13 weeks in duration in rodents and dogs which supported the chronic administration of inhaled treprostinil to patients. In addition, a two-year rat carcinogenicity study was performed with treprostinil inhalation at target doses up to 5.26, 10.6, and 34.1 mcg/kg/day which found no evidence for carcinogenic potential associated with inhaled treprostinil in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. Refer to the inhaled treprostinil Clinical Investigators Brochure for a full description of nonclinical data.

1.2.3 Clinical Experience

A series of acute and chronic investigator-initiated clinical studies were conducted with inhaled treprostinil to optimize the formulation for inhalation, determine dose response, tolerability, and safety and also to evaluate safety and tolerability when combined with other PAH therapies (Channick 2006, Voswinckel 2006). In the acute dosing studies, administration of inhaled treprostinil resulted in pulmonary vasodilation at relatively low doses. In the chronic studies, administration of inhaled treprostinil resulted in sustained improvement of exercise capacity.

A randomized, double blind, placebo controlled, Phase III study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil in combination with approved PAH therapies. Two hundred and thirty-five subjects who were clinically stable on an approved background oral PAH therapy (bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by six-minute walk distance (6MWD). At Week 12, subjects receiving inhaled treprostinil had a median improvement of +21.6 meters in 6MWD and subjects in the placebo group had a median improvement of +3.0 meters. The Hodges-Lehmann placebo-corrected median change from baseline in peak 6MWD was +20.0 meters (p=0.00044). The durability of this result was supported by secondary measures related to the trough 6MWD, which was measured at least four hours after the last dose of inhaled treprostinil. At Week 12, trough 6MWD showed a placebo-corrected median treatment effect of 13.7 meters (p=0.0066). The most commonly reported

adverse events (AEs) in the inhaled treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment related changes in vital signs, physical examination findings, chest x-rays, pulmonary function tests, or clinical laboratory parameters (McLaughlin 2010).

An open-label, extension study of the TRIUMPH-I study to evaluate the use of long-term inhaled treprostinil therapy was also conducted (TRIUMPH-OL). Subjects received one to 12 breaths (6 to 72 mcg) four times daily to achieve daily doses of 24 to 288 mcg. The longest duration of inhaled treprostinil exposure in the open-label study was 5.4 years and the mean duration 2.3 years. There were observed improvements in median 6MWD at 6, 12, 18, and 24 months of 28, 31, 32, and 18 meters, respectively. These data support the durability of improvement in 6MWD obtained with inhaled treprostinil as demonstrated during the double-blind phase of the study. Therapeutic benefit was also noted with improvements in the Borg dyspnea score, NYHA functional classification and quality of life (QOL). Survival was robust with one and two year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the trial. The most frequently reported AEs during the open-label study were cough (39%), headache (31%), upper respiratory tract infection (22%), and nausea (22%). There were no clinically significant changes in clinical chemistry or hematology parameters. Unique findings that related to the inhaled route of administration, in addition to cough, were throat pain and throat irritation, occurring in 12% and 10% of subjects, respectively. These events were usually of mild or moderate severity and transient in duration. In a few subjects, these specific AEs were more pronounced as six subjects (3%) discontinued inhaled treprostinil due to cough, including one subject (<1%) with dry throat (Benza 2011).

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Inhaled treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in patients with WHO Group I PH (McLaughlin 2010). Inhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity (Seeger 2013).

The use of inhaled prostacyclin therapy in patients with WHO Group 3 PH has been recently evaluated. In particular, Wang and colleagues (Wang 2015) reported data on 67 COPD patients with PH and found no change in arterial blood gases when a single dose of iloprost was administered during right heart catheterization (RHC). In addition, Bajwa and colleagues recently completed a prospective 16-Week study in nine COPD subjects with PH which reported no notable changes in arterial blood gases over the 16-Week treatment period (Bajwa submitted). Finally, Agarwal and colleagues (Agarwal 2015) recently presented data on 35 patients with WHO Group 3 PH who received treatment with inhaled treprostinil for six months. This retrospective review reported a mean increase from baseline in 6MWD of 61 meters with obstructive and restrictive patients reporting mean increases of 71 meters and 50 meters, respectively. Notably, this study also found that inhaled treprostinil was well tolerated with cough being the most commonly reported AE. Data from these recently

completed pilot studies suggest that inhaled treprostinil can be safely administered in patients with WHO Group 3 PH.

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE.

2 OBJECTIVES

To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE.

2.1 PRIMARY ENDPOINT

To evaluate the change in 6MWD measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. Change in peak 6MWD at Week 4
2. Change in peak 6MWD at Week 8
3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Time to clinical worsening from the time of randomization until one of the following criteria are met:
   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
5. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16

6. Change in distance saturation product (DSP) from Baseline to Week 16

2.4 SAFETY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. Adverse events (AEs)
2. Oxygenation
    a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2])
    b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
    a. Forced expiratory volume in one second (FEV_1)
    b. Forced vital capacity (FVC)
    c. Total lung capacity (TLC)
    d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalizations due to a cardiopulmonary indication
8. Exacerbations of underlying lung disease; defined as worsening of respiratory symptoms which require the modification or addition of systemic corticosteroids, antibiotics, or both.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multi-center, randomized, double-blinded, placebo-controlled, 16-Week, parallel group study. Subject eligibility will be based on inclusion and exclusion criteria described in Section 4. Approximately 314 eligible subjects will be randomized to study treatment in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤ 350 m and > 350 m). Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo screening assessments as described in Sections 7.1 and 7.3. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline pulmonary function tests (PFTs), 6MWT, and computed topography (CT) scan used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Baseline Visit: The Baseline assessments may be conducted over a 48 hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments (Sections 7.2 and 7.3), be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs, 6MWT, and CT scan used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Treatment Phase: The Treatment phase consists of five study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (at least 24 hours after the Week 15 visit [Final study visit/early termination [ET])]). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

A schedule of visits and assessments is presented in Section 3.2.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Study Procedures	Screening Phase	Baseline[1]	Combined Screening & Baseline Visit[1]	Treatment Phase				
Study Week				Week 4[2]	Week 8[2]	Week 12[2]	Week 15[2] (Trough 6MWD)	Week 16[2]/ Early Termination (at least 24 hours after Week 15)
Study Day	-30 to -1	1	1	29	57	85	106	113
Informed Consent	X		X					
Subject Eligibility[3]	X	X	X					
Medical History with PH History and Demographics	X		X					
SGRQ		X	X					X
Physical Examination	X		X					X
Vital Signs[4]	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments	X	X	X		X			X
N-terminal proBNP[5]		X	X		X			X
Blood sample for biomarker evaluation (optional)[6]		X	X					X
Serum Pregnancy Test[7]	X		X					
Urine Pregnancy Test[7]		X		X	X	X	X	X
12-Lead ECG		X	X					X
Peak 6MWT[8]	X	X	X	X	X	X		X
Trough 6MWT[9]							X	

Study Procedures	Screening Phase	Baseline[1]	Combined Screening & Baseline Visit[1]	Treatment Phase				
Study Week				Week 4[2]	Week 8[2]	Week 12[2]	Week 15[2] (Trough 6MWD)	Week 16[2]/ Early Termination (at least 24 hours after Week 15)
Pulse Oximetry[10]	X	X	X	X	X	X	X	X
Documentation of Supplemental Oxygen Requirement	X	X	X	X	X	X	X	X
PFTs[11]		X	X		X			X
Randomization		X	X					
Device Training		X	X					
Dosing instructions / Dosing / Accountability		X[17]	X[17]	X	X	X	X	X
Weekly Telephone/Email Contact[12]				---	---	---		
Adverse Events[13]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Concomitant Medications	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Hospitalizations[14]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Exacerbations of Underlying Lung Disease[15]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X
Time to Clinical Worsening[16]		X--	--X--	--X--	--X--	--X--	--X--	--X

ECG: electrocardiogram; N-terminal pro-brain natriuretic peptide; PFTs: pulmonary function tests; PH: pulmonary hypertension; SGRQ: St. George Respiratory Questionnaire; 6MWT: six-minute walk test

[1] Screening visit assessments can occur up to 30 days prior to the first dose of study drug. Baseline assessments can occur up to 48 hours prior to the first dose of study drug to allow for scheduling of all activities; however the Baseline 6MWT must be performed prior to but on the same day as the first dose of study drug. Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline

PFTs, 6MWT, and CT (if a historical scan within 6 months is not available) assessments used to determine eligibility criteria may be performed on the same day as but prior to the first dose of study drug.

[2] The visit window for Week 4, Week 8, Week 12, Week 15, and Week 16 is ± 5 days. The Week 16 visit must occur at least 24 hours after the Week 15 visit.

[3] For the Screening and Baseline visits, the subject must be evaluated for and meet all inclusion/exclusion criteria.

[4] Vital signs must be collected after five minutes of rest (seated); no other measurements or procedures should be performed during this five minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT then they should be obtained after recovery from the 6MWT.

[5] Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT and will occur prior to the first dose of study drug at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined.

[6] For subjects consenting to the optional biomarker sample.

[7] For females of childbearing potential. If the Screening and Baseline visits are combined, only a serum pregnancy test will be required.

[8] If the subject has not previously undergone a 6MWT at the study site, a practice test must be conducted at the Screening visit and must precede the Baseline 6MWT by at least one day. The Baseline 6MWT must precede the first dose of study drug. The Week 4, Week 8, Week 12, and Week 16 peak 6MWT must occur within 10 to 60 minutes after the most recent study drug dose. Prior to the start of each 6MWT the subject should rest (seated) for at least 10 minutes. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[9] The Week 15 trough 6MWT must occur at least four hours after the most recent study drug dose and at least 24 hours prior to the Week 16 visit. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[10] Pulse oximetry will be performed immediately prior to, during and immediately following each 6MWT. Pulse oximetry will include the measurement of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the eCRF. In addition, the lowest recorded SpO_2 obtained during each 6MWT will be recorded in the eCRF.

[11] PFTs will include the evaluation of FEV_1, FVC, TLC, and DLCO. In the event of a combined Screening/Baseline visit, Baseline PFTs should be performed prior to the first dose of study drug. PFTs should be performed after recovering from the Baseline, Week 8, and Week 16/ET 6MWTs.

[12] At least weekly telephone contact is required throughout the study (may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in clinic for clinically significant AEs or other emergent issues.

[13] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed and should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit (Week 16).

[14] Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration, should also be recorded as SAEs per Appendix 15.2.

[15] Exacerbations of underlying lung disease; defined as worsening of respiratory symptoms which require the modification or addition of systemic corticosteroids, antibiotics, or both. Exacerbations will also be recorded as AEs or SAEs per Appendix 15.2.

[16] Time to clinical worsening will be measured from the time of randomization until one of the following criteria are met: Hospitalization due to a cardiopulmonary indication, decrease in 6MWD > 15% from Baseline directly related to the disease under study, at two consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation.

[17] Once all entry criteria have been met and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a one hour observation period (Defined as Day 1).

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 Six-Minute Walk Test (6MWT)

The 6MWT is a validated and reliable measure of exercise capacity in patients with chronic respiratory diseases (Holland 2014). This study will utilize an unencouraged 6MWT to minimize potential bias associated with encouragement. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements as described in Appendix 15.1. Prior to the start of each 6MWT the subject must rest (seated) for at least 10 minutes. This 6MWT protocol applies to practice (if applicable), Baseline, and treatment 6MWTs. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments. Pulmonary rehabilitation may not be introduced to a subject's treatment regimen between Baseline (first dose of study drug) and Week 16. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.1 Practice Six-Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course intended for use during the study. Subjects who have not previously performed the 6MWT at the study site on the course intended for use during the study, must perform a practice 6MWT at the study site at least one day prior to the Baseline Visit.

3.3.1.1.2 Baseline Six-Minute Walk Test

Baseline 6MWT must be performed in the following fashion: a) prior to initiation of study drug and b) on the day of randomization (*i.e.,* the Baseline Visit on same day but prior to the first dose of study drug). Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

Note: The Baseline 6MWT (not the practice 6MWT) will determine the subject's eligibility to participate in the study (6MWD $\geq$ 100 meters per inclusion criteria).

3.3.1.1.3 Treatment Six-Minute Walk Tests

3.3.1.1.3.1 Peak Six-Minute Walk Tests

Peak 6MWTs will be conducted at Weeks 4, 8, 12, and 16/ET. The 6MWT must be conducted between 10 to 60 minutes after the most recent dose of study drug. If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments. The Week 16 peak 6MWT should occur at least 24 hours after the Week 15 visit. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.3.2 Trough Six-Minute Walk Test

A trough 6MWT will be performed during the Week 15 visit. The trough 6MWT must be performed at least four hours after the most recent dose of study drug and at least 24 hours prior to the end of study visit (Week 16). If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.2 St. George's Respiratory Questionnaire

The SGRQ will be conducted at Baseline (prior to study drug) or as part of the Screening visit assessment if the Screening and Baseline visits are combined and at Week 16 (or ET for those subjects discontinuing the study prematurely). The SGRQ should be completed as the first assessment during these visits (after informed consent is obtained) before the subject completes any of the other scheduled visit assessments. A copy of the SGRQ can be found in Appendix 15.3.

3.3.1.3 N-terminal pro-brain natriuretic peptide (NT-proBNP)

Plasma NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). NT-proBNP sample collection will occur at Baseline (or as part of the Screening visit assessment if the Screening and Baseline visits are combined) prior to starting study drug, at Week 8, and at Week 16/ET. Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT.

3.3.1.4 Optional Biomarker

For subjects consenting to the optional biomarker sample, blood will be collected for the evaluation of biomarkers (specific targets to be determined) at Baseline and at Week 16/ET.

3.3.1.5 Time to Clinical Worsening

Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:

a. Hospitalization due to a cardiopulmonary indication
b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
c. Death (all causes)
d. Lung transplantation

Because there are no Food and Drug Administration (FDA) approved therapies for the treatment of WHO Group 3 PH, subjects experiencing clinical worsening will remain on study therapy for the duration of the study (or until criteria for study termination are met per Section 8.1 of the protocol). Subjects experiencing death or lung transplantation will be discontinued from the study per Section 8.1 of the protocol.

3.3.1.6 Change in DSP

Change in DSP is the product of distance walked and lowest oxygen saturation recorded during the 6MWT. This assessment has been shown to be predictive of mortality in patients with idiopathic pulmonary fibrosis and as such will be evaluated as an exploratory endpoint in this study (Lettieri 2006). Change from Baseline to Week 16 in DSP will be calculated.

3.3.2 Safety

During this study, treatment emergent changes in physical examination (PE) findings, vital signs, clinical laboratory parameters, ECG parameters, PFTs, oxygenation, and the development of AEs after treatment will be the primary assessments of safety. Hospitalizations due to cardiopulmonary indications will also be recorded from the time of informed consent until study termination (or ET for those subjects discontinuing the study prematurely). Exacerbations of underlying lung disease will also be recorded from the time of informed consent until study termination.

3.3.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PH history, and PE will be conducted during Screening. If any changes to the medical history occur between the Screening and Baseline visit, those should be recorded. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs should be recorded. Any significant changes to the subject's medical condition and PE must be documented throughout the course of the study. A complete PE will also be conducted by appropriate study personnel (as documented on the Delegation of Authority Log) at the Week 16/ET visit. Any clinically significant changes from Baseline noted during the Week 16/ET PE should be reported as AEs.

3.3.2.2 Vital Signs

Vital signs will be assessed at Screening, Baseline, each subsequent study visit, and at Study Termination. Vital signs measured will include blood pressure (systolic and diastolic), heart rate (HR), respiratory rate (RR), temperature, and weight. Height will be assessed at Baseline only. Vital signs must be assessed following at least five minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures should be performed during this five-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, they should be obtained after recovery of the 6MWT. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms.

3.3.2.3 12-Lead ECG

A 12-lead ECG will be recorded after at least five minutes of rest in the semi-recumbent position at Baseline (prior to study drug) and repeated at the Week 16/ET visit. Recordings should include lead II as a rhythm strip and contain at least five QRS complexes. ECG parameters to be collected include rhythm, HR, PR interval, QT interval, QRS duration, and any clinically significant abnormalities.

3.3.2.4 Clinical Laboratory Assessments

The results of all clinical laboratory tests conducted at Screening and Baseline must be assessed by the Investigator to determine each subject's eligibility to participate in the study prior to starting study drug. Screening and Baseline clinical laboratory assessments can be combined into a single blood draw if all eligibility criteria are met within 48 hours prior to the first dose of study drug at Baseline. Central laboratory data are ultimately used to qualify subjects for the study. However, for subjects who are well known to the Investigator and who are clinically stable, the Investigator may confirm eligibility using local laboratory values so as not to delay randomization while waiting for central laboratory results if the Screening and Baseline visits are combined.

Clinical laboratory results outside the normal reference range must be assessed for clinical significance by the Investigator. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status.

Clinically significant abnormal laboratory test values will be reported as AEs and treated and/or followed-up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator. Where appropriate, medical tests and examinations will be performed to assess and document resolution.

3.3.2.4.1 Clinical Chemistry and Hematology

Blood for the measurement and evaluation of clinical chemistry and hematology, will be collected at the Screening and Baseline visits prior to administration of study drug and repeated at Week 8 and Week 16/ET to assess for treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Values for the following parameters will be obtained:

Electrolyte Panel

- Sodium
- Potassium
- Bicarbonate
- Chloride

Chemistry Panel

- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Urea nitrogen
- Creatinine
- Calcium
- Albumin

Hematology Panel

- Hemoglobin
- Hematocrit
- Red blood cell count
- Red blood cell morphology
- White blood cell count
- Platelet count

3.3.2.4.2 Pregnancy Testing

Females of childbearing potential will undergo a serum pregnancy test at Screening followed by urine pregnancy tests at Baseline and each subsequent study visit. A serum pregnancy test will be collected at the Screening Visit (or Baseline visit if the Screening and Baseline visits

are combined). A positive pregnancy test will exclude the subject from further participation in the study. Pregnant subjects who are discontinued from the study will be transitioned to an alternate therapy at the discretion of the Investigator.

3.3.2.5 Pulmonary Function Tests (PFTs)

Pulmonary Function Tests (PFTs) will be assessed at Baseline and repeated at Week 8 and Week 16/ET. Baseline PFTs are to be conducted prior to the first dose of study drug and after recovery from 6MWT. The Week 8 and Week 16/ET PFTs should be conducted after recovery from the 6MWT. If the PFTs are done both prior to and after a bronchodilator, only the pre-bronchodilator values will be recorded.

The following parameters will be recorded (absolute values and % predicted): FEV_1, FVC, TLC, and DLCO (uncorrected and corrected for hemoglobin).

3.3.2.6 Oxygenation

3.3.2.6.1 Pulse Oximetry

Pulse oximetry will be assessed immediately prior to, throughout the conduct of, and immediately after each scheduled 6MWT assessment at Baseline, Week 4, Week 8, Week 12, Week 15, and Week 16/ET. Pulse oximetry will also be performed during the practice 6MWT assessment as applicable. Pulse oximetry will include the collection of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the electronic case report form (eCRF). In addition, the lowest recorded SpO_2 (and associated HR) obtained during each 6MWT will be recorded in the eCRF.

3.3.2.6.2 Supplemental Oxygen Requirement

The amount of supplemental oxygen (L/min) required at rest will be assessed at Baseline and at regularly scheduled visits. The amount of supplemental oxygen required at the 6MWT assessment will also be recorded for each 6MWT assessment.

3.3.2.7 Adverse Events

Adverse events will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed. Each subject will be questioned for AEs at each scheduled study visit and during required telephone/email contacts. Subjects will also be instructed to spontaneously report all AEs throughout the study.

All AEs should be followed until either resolution (or return to normal or Baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for serious (*i.e.,* serious adverse events [SAEs]) should be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 30 days after completion of the

final study visit (Week 16/ET). All AEs/SAEs that occur while the subject is on study drug will be recorded as instructed in this protocol.

Sections 9 and 15.2 provide the guidelines and definitions for recording AEs.

3.3.2.8 Concomitant Medications

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, should be recorded in the subject's source documents and captured in the eCRF as required.

3.3.2.9 Hospitalization due to Cardiopulmonary Indications

Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration should also be recorded as SAEs per Appendix 15.2. Please note that, when possible, study medication should be continued during hospitalizations.

3.3.2.10 Exacerbations of Underlying Lung Disease

Exacerbations of underlying lung disease are defined as the worsening of respiratory symptoms which require the modification or addition of systemic corticosteroids, antibiotics, or both. Exacerbations of underlying lung disease should be recorded throughout the duration of the study from the time of informed consent until study termination. Exacerbations of underlying lung disease will also be reported as AEs or SAEs per Appendix 15.2.

3.3.2.11 Weekly Telephone/Email Contact

Weekly telephone/email contact is required throughout the 16 week study to instruct the subject to titrate their dose of study drug and to assess for AEs and concomitant medications. Weekly telephone/email contact may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). The subject may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All telephone or email contacts (*i.e.*, any dosing instructions, AEs reported and/or medication changes) with the subject must be noted in the source documentation.

3.4 NUMBER OF SUBJECTS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (two-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

3.5 NUMBER OF CENTERS

This study is a multi-center with approximately 75 participating study centers.

3.6 ESTIMATED STUDY DURATION

From Screening until study completion, expected duration of study participation is approximately 20 weeks (includes a four week Screening period and 16 week treatment period).

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during the Screening period and reconfirmed at the Baseline visit prior to the first dose of study drug. Study related procedures must be conducted during the Screening period after obtaining informed consent to determine subject eligibility for the study.

4.1 INCLUSION CRITERIA

1. Subject voluntarily gives informed consent to participate in the study.
2. Males and females aged 18 – 79 years at the time of informed consent.
    a. Females of reproductive potential[1] must be non-pregnant (as confirmed by a serum pregnancy test at screening) and non-lactating, and will:
        i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
        ii. Use two medically acceptable, highly-effective forms of contraception[2] for the duration of study, and at least 30 days after discontinuing study drug.
    b. Males must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.

[1] Females who are successfully sterilized (surgical sterilization methods include hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (defined as amenorrhea for at least 12 consecutive months) are not considered to be of reproductive potential.

[2] Medically acceptable, highly-effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), and barrier methods (such as a condom or diaphragm) when used with a spermicide. For women of reproductive potential, a negative pregnancy test is required at Screening and Baseline prior to initiating study drug.

3. The subject has a confirmed diagnosis (based on CT imaging and PFTs performed within six months prior to the first dose of study drug) of WHO Group 3 PH associated with one of the following:
    a. Idiopathic interstitial pneumonia (IIP) including:
        i. Idiopathic pulmonary fibrosis (IPF)

ii. Idiopathic nonspecific interstitial pneumonia
iii. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)
iv. Desquamative interstitial pneumonia (DIP)
v. Cryptogenic organizing pneumonia (COP)
vi. Acute interstitial pneumonitis (AIP)
vii. Idiopathic lymphoid interstitial pneumonia
viii. Idiopathic pleuroparenchymal fibroelastosis
ix. Unclassifiable idiopathic interstitial pneumonia

b. Chronic hypersensitivity pneumonitis (CHP)
c. Occupational lung disease (drug or radiation-induced)
d. Combined pulmonary fibrosis and emphysema (CPFE)

4. Subjects are required to have a RHC within one year prior to the first dose of study drug with the following documented parameters:
   a. Pulmonary vascular resistance (PVR) ≥ 4 Wood Units (WU) and
   b. A left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) of ≤ 12 mmHg if PVR ≥ 4 WU to < 6.25 WU or ≤ 15 mmHg if PVR ≥ 6.25 WU and
   c. A mean pulmonary arterial pressure (mPAP) of ≥ 30 mmHg

Note: For subjects receiving background therapy with an FDA approved medication (i.e., endothelin receptor antagonist [ERA], phosphodiesterase type-5 inhibitor [PDE-5I], or soluble guanylate cyclase stimulator [sGC]) for PAH, the RHC must be performed after the initiation of aforementioned PAH therapy to ensure the subject meets the required RHC parameters.

5. An uncorrected diffusing capacity of the lungs for carbon monoxide (DLCO) of < 50%.
6. Baseline 6MWD ≥ 100 meters.
7. The subject is either not receiving any PAH-approved oral therapy (ERA, PDE-5I, or sGC), or is receiving monotherapy (ERA, PDE-5I, or sGC) for at least 90 days and receiving a stable dose for ≥ 30 days prior to randomization.
8. Subjects on a chronic medication for underlying lung disease must be on a stable and optimized dose for ≥ 30 days prior to the first dose of study drug. Subjects receiving pirfenidone or nintedanib must have been receiving treatment for at least 90 days and on a stable dose for at least 30 days prior to the first dose of study drug.
9. Subjects on a supportive medication therapy (*e.g.,* anticoagulants, diuretics, oxygen, etc.) must be on a stable and optimized dose for ≥ 30 days prior to the first dose of study drug. Exceptions are the discontinuation or dose changes of anticoagulants and / or dose change of diuretics.

10. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.

4.2 EXCLUSION CRITERIA

1. The subject has a diagnosis of PAH or PH for reasons other than ILD as outlined in inclusion criterion 3. This would include, but is not limited to, the concomitant presence of thromboembolic disease (acute or chronic), untreated or inadequately treated obstructive sleep apnea (OSA), sarcoidosis, human immunodeficiency virus (HIV)-1 infection, toxin exposure such as methamphetamine or anorexigen use, and other conditions of the WHO Group I, II, IV, and V classification.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any prostacyclin therapy (i.e., epoprostenol, treprostinil, iloprost, or beraprost) within 30 days of informed consent, except for acute vasoreactivity testing.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
   a. LVEDP or PCWP > 15 mmHg (or >12 if PVR ≥ 4 to < 6.25 WU)
   b. Left ventricular ejection fraction < 40% as assessed by either multigated angiogram (MUGA), angiography or echocardiography.

   Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) will not be excluded.
5. Subjects must not have three or more of the following left ventricular disease/dysfunction risk factors:
   a. Body Mass Index (BMI) ≥ 30 kg/m^2
   b. History of Essential Hypertension
   c. Diabetes Mellitus – any type
   d. Historical evidence of significant coronary disease established by any one of the following:
      i. history of myocardial infarction or percutaneous coronary intervention or angiographic, or
      ii. evidence of coronary artery disease (> 50% stenosis in at least one coronary artery), or
      iii. positive stress test with imaging, or previous coronary artery bypass graft, or stable angina
6. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
7. Use of any inhaled tobacco products or significant history of drug abuse within six months prior to first dose of study drug.

8. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of the first dose of study drug.
9. Initiation of pulmonary rehabilitation within 12 weeks prior to the first dose of study drug.
10. The subject has uncontrolled systemic hypertension as evidenced by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
11. The subject has any form of congenital heart disease or congenital heart defect (repaired or unrepaired) (other than a patent foramen ovale [PFO]).
12. The subject has anemia as defined by a screening hemoglobin value < 9.0 g/dL, active infection, or any other condition that would interfere with the interpretation of study assessments.
13. The subject has a Body Mass Index ≥ 40 kg/m^2.
14. The subject has any musculoskeletal disorder (*i.e.,* arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), is using a device to assist walking (*i.e.,* cane or walker), or has any other condition that would limit ambulation.
15. Use of any investigational drug/device, or participation in any investigational study within 30 days prior to the first dose of study drug.

4.3 PRESCRIBED THERAPY

Subjects must not be receiving any prostacyclin (i.e., epoprostenol, treprostinil, iloprost, beraprost, or any other prostacyclin therapy) within 30 days prior to informed consent (unless used for acute vasoreactivity testing). Subjects can either be on no FDA approved PAH background therapy or on a single FDA approved PAH therapy including: an ERA, a PDE-5I, or a sGC so long as they have been receiving treatment for a minimum of 90 days and on a stable dose for at least 30 days prior to randomization.

Subjects on a supportive therapy (*e.g.,* anticoagulants, diuretics, oxygen) must have been on a stable and optimized dose for ≥ 30 days prior to the first dose of study drug. Exceptions are the discontinuation or dose changes of anticoagulants and / or dose change of diuretics. Subjects on a chronic medication for underlying lung disease should be on a stable and optimized dose for ≥ 30 days prior to the first dose of study drug. Subjects receiving pirfenidone or nintedanib should have been receiving treatment for a minimum of 90 days and at the current dose for at least 30 days prior to the first dose of study drug. Subjects may not newly initiate pirfenidone or nintedanib from the first dose of study drug (Baseline) through study termination.

Subjects may not initiate pulmonary rehabilitation (rehab) within 12 weeks prior to the first dose of study drug until the end of the study (Week 16).

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, should be recorded in the subject's source documents and transcribed into the eCRF as required. The flow rate of supplemental oxygen should be recorded as outlined in Section 3.3.2.6.2.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo.

5.2 RANDOMIZATION

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo. An IXRS will be utilized for the central randomization procedure. Sites will enter values of the qualifying 6MWT and the date the test was conducted into the IXRS and will be notified if the subject qualifies for the study.

All subjects will be randomized using a centrally administered stratified permuted block randomization, stratified by Baseline 6MWD (≤ 350 m and > 350 m) and receipt of background FDA approved therapy for PAH (i.e., treatment naïve or receiving an FDA approved therapy for PAH [i.e., ERA, PDE-5I, or sGC]).

5.3 BLINDING

The Investigator, study site, subject and Sponsor will not be aware of the treatment allocation. All clinical trial material will be provided as blinded study drug.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION AND SCHEDULE

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Placebo will be provided as an identical solution that will be inhaled using the same ultrasonic nebulizer. All subjects will receive study drug (inhaled treprostinil or placebo) using the commercially available TD-100 ultrasonic nebulizer (Tyvaso Inhalation System). Subjects will be trained on inhalation of study drug using the nebulizer device. Detailed instructions for the use of these devices will be provided to all study subjects. In addition, all subjects will receive a copy of the commercially available Tyvaso Inhalation System Instructions for Use (IFU) for the TD-100 ultrasonic nebulizer.

Once informed consent has been signed, all entry criteria have been met, and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a one hour observation period (defined as Day 1). Study drug doses should be maximized throughout the study, dose escalations (additional one breath four times daily) can occur up to every three days with a target dosing regimen of 9 breaths (54 mcg) four times daily and a maximum of 12 breaths (72 mcg) four times daily within four weeks of beginning the treatment. Table 6-1 provides a guideline for recommended dose escalations.

Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table

Study Day[1]	Single Dose	Total Daily Dose
Titrating to maximum dose of 12 breaths		
1-3	3 breaths QID (18 mcg)	72 mcg
4-6	4 breaths QID (24 mcg)	96 mcg
7-9	5 breaths QID (30 mcg)	120 mcg
10-12	6 breaths QID (36 mcg)	144 mcg
13-15	7 breaths QID (42 mcg)	168 mcg
16-18	8 breaths QID (48 mcg)	192 mcg
19-21	9 breaths QID (54 mcg)	216 mcg
22-24	10 breaths QID (60 mcg)	240 mcg
25-27	11 breaths QID (66 mcg)	264 mcg
28 (and beyond)	12 breaths QID (72 mcg)	288 mcg

* QID: four times daily; mcg: micrograms
[1] Study day refers to the days on study drug with Day 1 referring to the first dose of study drug.

The dosing schedule is recommended as a guide only. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and functional improvement.

If subjects are unable to tolerate the initial three breaths, they may decrease their next dose to one or two breaths of study drug (as determined by the Investigator) four times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of three breaths and titrate to a target of 9 breaths and a maximum dose of 12 breaths four times a day during waking hours, as tolerated.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject should occur prior to each dose adjustment or at least weekly to monitor for AEs, clinical worsening events and make decisions about dose titration.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, the site personnel, subject, and Sponsor will remain blinded to the treatment assignment of all subjects. A medical emergency (*e.g.,* a life threatening event) constitutes the only reason for unblinding during the treatment phase. Appropriate communications must take place between the site and the Sponsor before accessing the IXRS to allow unblinding of a subject's treatment assignment.

6.3 COMPLIANCE

Each subject will be provided with a dosing diary in order to record dosing information from Randomization until Week 16/ET. Subjects will be required to bring the completed dosing diary and all empty and unused study drug ampoules to each scheduled study visit. At each visit, all study drug returned by the subject (used and unused) will be collected and new study

drug will be dispensed. The appropriate study personnel must document the number of used and unused ampoules and determine if the appropriate amount of study drug remains based on the dose of study drug prescribed.

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each study visit, the subject will be asked whether he or she has been compliant with dosing instructions. If it is determined that a subject is not compliant with study drug then site personnel must re-educate the subject on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor.

7 EXPERIMENTAL PROCEDURES

Screening may begin up to 30 days prior to first dose of study drug. Baseline assessments may be conducted over a 48 hour period prior to the first dose of study drug to allow for scheduling of all activities. Alternately, the Screening and Baseline assessments may be conducted in one visit if all assessments are performed and all entry criteria are satisfied within the 48 hours prior to randomization and first dose of study drug.

7.1 SCREENING VISIT

The recommended sequence of assessments for the Screening visit is as follows (if not combined with the Baseline visit [See Section 7.2 for the recommended sequence of events for the combined Screening/Baseline visit]):

- Informed consent
- Inclusion/exclusion criteria review
  - If necessary, the following procedure may be performed during the 30 day Screening window if required to satisfy inclusion/exclusion criteria (previous medical records documenting eligibility criteria may also be used provided the previous records document subject eligibility within the protocol mandated timelines, as applicable):
    - RHC (Must be performed within one year prior to the first dose of study drug and after initiating PAH background therapy [if applicable]. If a historical RHC is not available in this timeframe, a RHC may be performed during Screening so long as it is performed at least five days prior to the first dose of study drug [Baseline (Day 1)]; a RHC cannot be combined with the Baseline visit)
    - CT scan (must be performed within six months prior to the first dose of study drug)
- Demographics
- PH history
- Medical history
- Physical exam

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT, if practice 6MWT is applicable) including: height, weight, RR, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature.
- Serum pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- Practice 6MWT (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT, if applicable)
- Documentation of supplemental oxygen requirement (L/min)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications

7.2 BASELINE/RANDOMIZATION VISIT

All Baseline assessments must be performed prior to the first dose of study drug. Baseline assessments may be conducted over a 48 hour period prior to the first dose of study drug to allow for scheduling of assessments; however, the Baseline 6MWT must occur on the same day as but prior to the first dose of study drug. The recommended sequence of assessments for the Baseline visit is as follows (if not combined with the Screening visit):

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- 12-lead ECG (following at least five minutes of rest in the semi-recumbent position)
- Documentation of supplemental oxygen requirement (L/min)
- 6MWT (must be conducted prior to first dose of study drug on the day of randomization; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to first dose of study drug and after recovery from the Baseline 6MWT)
- Hospitalizations due to a cardiopulmonary indication

- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least one hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation

7.3 COMBINED SCREENING AND BASELINE

The Screening and Baseline assessments may be conducted in one visit if all assessments are performed and all entry criteria are satisfied within 48 hours prior to randomization and dosing of study drug. Baseline PFTs, 6MWT, and CT (if a historical assessment is not available within six months prior to the first dose of study drug) assessments used to determine eligibility criteria may be performed on the same day but prior to the first dose of study drug. The recommended order of assessments for a combined Screening and Baseline Visit is outlined below.

<u>Assessments to be completed as part of the Screening phase</u>:

- Informed consent
- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Inclusion/exclusion criteria review
- Blood draws for clinical laboratory parameters and serum pregnancy test (enough blood should be drawn for local laboratory to confirm the entry criteria for hemoglobin and serum pregnancy test [as applicable], as well as for the complete panel for central laboratory processing)
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Demographics
- PH history
- Medical history

- Physical examination
- Vital Signs (following at least five minutes of rest; collected prior to the 6MWT or after recovery from the 6MWT) including: weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Practice 6MWT to be conducted one day prior to Baseline assessments (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Adverse events
- Concomitant medications

Assessments to be completed as part of the Baseline Visit:

- 12-Lead ECG (following at least five minutes of rest in the semi-recumbent position)
- 6MWT (must be conducted on the same day as but prior to first dose of study drug; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to first dose of study drug and after recovery from the Baseline 6MWT).
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least one hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation

7.4 TREATMENT PHASE: WEEKS 4, 8, AND 12

The following assessments to be completed during the Treatment phase:

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from 6MWT)
- Documentation of supplemental oxygen requirement (L/min)

- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters (Week 8 only)
- NT-proBNP (for central laboratory processing only [Week 8 only])
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (Week 8 only; to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart.
  - Death (all causes)
  - Lung transplantation
- Adverse events
- Concomitant medications
- Study drug accountability

Please note the visit window for the Week 4, Week 8, and Week 12 visits is ± 5 days.

7.5 TREATMENT PHASE: WEEK 15 (TROUGH)

- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT)
- Documentation of supplemental oxygen requirement (L/min)
- Urine pregnancy test, for women of childbearing potential
- Trough 6MWT (at least four hours after the last dose of study drug)
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
  - Death (all causes)

- Lung transplantation

- Adverse events
- Concomitant medications
- Dosing instructions/study drug accountability

Please note the visit window for the Week 15 visit is ± 5 days and at least 24 hours prior to the Week 16 visit.

7.6 END OF STUDY (WEEK 16) OR EARLY TERMINATION (ET) VISIT

The assessments to be completed during the Week 16 visit are listed below in recommended sequence of events. If a decision is made to early terminate a subject, the following assessments should be conducted as soon as possible and prior to study drug discontinuation, if possible:

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Physical examination
- Vital signs (following at least five minutes of rest; collected prior to 6MWT or after recovery from the 6MWT)
- Documentation of supplemental oxygen requirement (L/min)
- 12-Lead ECG (following at least five minutes of rest in the semi-recumbent position)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation
- Adverse events

- Concomitant medications
- Study drug accountability

Subjects who remain on study drug, complete all assessments during the 16 week Treatment Phase, and who meet all eligibility criteria for the open-label extension study (RIN-PH-202) are eligible for an open-label extension study (RIN-PH-202). Subjects who permanently discontinue study drug during the 16 week Treatment Phase are not eligible for entry in the open-label extension study.

7.6.1 Study Contacts

During the treatment phase, all subjects will be contacted at least once a week via telephone or email (or more often as needed) to follow-up on adherence of the correct dose titration of study drug, and to assess for AEs and concomitant medications. A copy of emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All study contacts (*i.e.,* any dosing instructions, AEs reported, and/or medication changes) with the subject will be recorded.

The weekly study contacts may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or be withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue study drug to protect the safety of the subject.
- The subject consistently deviated from the protocol.
- Lung transplantation.
- The subject becomes pregnant.
- The subject's behavior is likely to undermine the validity of his/her results.

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF and complete the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues study drug prematurely due to an AE, the subject will be followed until either the Investigator determines that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 30 days if the AE extends beyond the final visit.

8.2 LOST TO FOLLOW-UP

If a subject fails to return to clinic or respond after at least three documented attempts by the site to contact the subject by telephone or email, the Investigator should issue a written letter by certified mail requesting the subject to contact the clinic. If no response is received, the subject will be considered lost to follow-up. The site will record the last date of contact in the eCRF as the termination date.

8.3 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of the Investigator and/or Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs, or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.4 CRITERIA FOR DISCONTINUING THE SITE

The study may also be terminated at a given site if:

- The Investigator elects to discontinue the study.
- The Sponsor elects to discontinue the study at the site.
- U.S. FDA, European, or national regulations are not observed.
- The protocol is consistently violated.
- Changes in personnel or facilities adversely affect performance of the study.

9 ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the use of the medicinal product.

An AE may include:

- An intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance.
- A worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (*e.g.,* exacerbation of a pre-existing illness following the start of the study or an increase in frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by the use of the term "adverse event".

An AE does not include the following:

- Medical or surgical procedures (*e.g.,* surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an AE.
- Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not AEs.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (*e.g.,* hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- The disease or disorder being studied or a sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is an AE occurring at any time after informed consent that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Results in a medically important event of reaction

Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is

also to be documented in the eCRF (see Appendix 15.2 for definitions). Where possible, AEs should be recorded using standard medical terminology. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. If several signs or symptoms are clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

9.3 FOLLOW UP OF ADVERSE EVENTS

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than four weeks after completion of the final study visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with any new or additional information as appropriate.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the Sponsor by fax/email (+ 1 919-313-1297 or drugsafety@unither.com) within 24 hours of awareness. A completed SAE Notification Report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corporation. A follow-up SAE Notification Report form must be forwarded to Global Drug Safety at United Therapeutics Corporation within 24 hours of the receipt of any new or updated information. The Investigator must also promptly notify their Investigational Review Board (IRB) or Ethics Committee (EC) of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

9.5 PREGNANCY

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via fax or e-mail to Global Drug Safety at United Therapeutics Corporation (+ 1 919-313-1297 or drugsafety@unither.com). The United Therapeutics Global Drug Safety department will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification Form. Pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

9.6 SAFETY REPORTS

In accordance with national regulations, the sponsor will notify the appropriate regulatory authority(ies), and all participating Investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report

these AEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion, or study discontinuation for any reason. A representative from the sponsor will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated and the database will be edited as appropriate. The eCRF screens are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify his/her approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject's eCRF by the site after the Investigator initially signs the eCRF. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (two-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

10.3 ANALYSIS PLAN

Details of the efficacy and safety analyses are provided below. A separate statistical analysis plan will document further details of the statistical methods to be employed, including any changes to planned analyses specified within this protocol. The analysis plan will be finalized prior to any unblinding of study data by the Sponsor. Unless otherwise specified, all statistical tests will be two-sided at alpha level of 0.05. All statistical calculations will be completed using the latest version of SAS®.

The Intent-to-Treat (ITT) population will be defined as all subjects randomized into the study; all ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were actually given. All efficacy analyses will be performed on this ITT population, unless otherwise specified. The Safety population will be defined as all subjects enrolled into the study who received at least one dose of study drug; all safety population subjects will be counted in the group corresponding to the study drug actually received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

10.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between two treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.

10.3.2 Secondary Efficacy Endpoints

The effect of inhaled treprostinil will be formally tested on the following three secondary efficacy endpoints:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of NT-proBNP from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

The similar approach for the analysis of primary efficacy endpoint will be used. No adjustment for multiplicity is planned.

10.3.3 Exploratory Endpoints

The effect of inhaled treprostinil will be evaluated on the following parameters:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD at from Baseline to Week 8
3. Change in SGRQ from Baseline to Week 16
4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until one of the following criteria are met:
    a. Hospitalization due to a cardiopulmonary indication
    b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at two consecutive visits and at least 24 hours apart
    c. Death (all causes)
    d. Lung transplantation
5. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16
6. Change in distance saturation product (DSP) from Baseline to Week 16

For changes in peak 6MWD and SGRQ, a similar approach for the analysis of primary efficacy endpoint will be used. For time to clinical worsening, Kaplan-Meier estimator will be provided and log-rank test will be used to compare the treatment difference.

10.3.4 Safety Analyses

The safety of inhaled treprostinil will be evaluated by comparison of the following parameters between the two treatment groups:

1. AEs
2. Oxygenation
    a. Pulse oximetry (SpO_2)
    b. Supplemental oxygen (L/min) requirement
3. Pulmonary function:
    a. FEV_1
    b. FVC
    c. TLC
    d. DLCO
4. Clinical laboratory parameters
5. Vital signs
6. 12-Lead ECG
7. Hospitalizations due to cardiopulmonary indications
8. Exacerbations of underlying lung disease; defined as worsening of respiratory symptoms which require the modification or addition of systemic corticosteroids, antibiotics, or both.

All AEs as recorded by the Investigators will be assigned a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class by the Sponsor for reporting purposes. The summary of AEs will include the number and percentage of subjects, as well as the number of events reported for each preferred term. No inferential analyses are planned for the AEs.

Data collected prior to dosing will serve as Baseline values for the evaluation of data collected during the treatment phase. Summary statistics will be calculated for measured values and changes from Baseline values. Treatment-emergent changes in vital signs, ECGs, PFTs, oxygenation parameters and clinical laboratory parameters will be summarized by treatment group. Incidence of hospitalization due to cardiopulmonary indications and exacerbations of underlying lung disease will be summarized by treatment group. No inferential analyses are planned on these safety endpoints.

10.4 INTERIM ANALYSES

Interim analyses for safety data will be performed at the request of the Data Monitoring Committee (DMC). Interim analyses for efficacy data are not planned for this study.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the clinical study report.

10.7 DATA MONITORING COMMITTEE

A DMC will be established for the study including physicians knowledgeable in the treatment of PH. Throughout the course of the study the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DMC charter. The DMC will be blinded to individual subject treatment allocation during the review process. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The sponsor will only have access to blinded study data during this process.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

11.1.1 Study Drug

The Sponsor will supply study medication (treprostinil inhalation solution, 0.6 mg/mL or placebo), as clear liquid in 2.9 mL ampoules. The ampoules will be packaged in groups of four, sealed in aluminum pouches. There will be nine pouches per carton.

11.1.2 Study Device

The Sponsor will supply commercially available TD-100 nebulizers (Tyvaso Inhalation System®) and accessories to the site in standard packaging labeled with the study number. The Tyvaso Inhalation will also be provided with the commercially available Instructions for Use (IFU).

Each subject will receive two nebulizers at the start of the study. In addition, the subjects will be provided with a month worth of plastic accessories at each study visit.

11.2 LABELING

11.2.1 Study Drug

The foil pouch and the outer carton will each be labeled with the same information and sent to the site. At a minimum, the study medication outer packaging (pouch and carton) will be labeled to disclose clearly the product name, study number, kit identification number, expiry date, Sponsor's name and address, instructions for use, and storage information (subject to regulatory requirements in each study region or country).

11.2.2 Study Device

Study subjects will receive commercially available TD-100 nebulizers and accessories separately from study drug. Study subjects will receive two devices at Baseline supplied as a device starter kit. Subjects will receive replacement parts as part of a monthly device

resupply kit. The nebulizers and accessories will be supplied using standard packaging labeled with the study number.

11.3 STORAGE AND HANDLING OF CLINICAL TRIAL MATERIAL (CTM)

All study drug will be stored at room temperature 25°C (77°F) with excursions permitted to 15°C-30°C (59°F – 86°F). Study drug should not be frozen, refrigerated, or exposed to heat. Keep the ampoules in the foil pouch to protect from light. Once the foil pouch is opened, use within seven days. See investigational medicinal product label for information on use and storage of the product.

Study drug will be stored in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study drug to any subject not participating in this protocol.

11.4 SUPPLY AND RETURN OF CTM

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At Baseline, an IXRS will be utilized to randomize the subjects and assign the appropriate study drug for the first four-week treatment interval. At subsequent study visits, the IXRS will be utilized by study staff to assign subsequent study drug kits to the subjects based upon their current treatment allocation. At each study visit, all study drug dispensed to a subject should be returned to the study site, including all used and unused ampoules.

At the end of the study, nebulizers used during the study should be collected from each subject not continuing into the open-label extension study. Subjects continuing into the open-label extension study will retain their devices for use in the open-label extension study.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records include, but are not limited to: the amount of study drug received from the sponsor, the amount dispensed to each subject, and the amount of used/unused study drug returned to the site from the subject.

At each visit, site personnel will:

- Collect and document all study drug returned by the subject (both used and unused).
- Compute study drug compliance using the dosing instructions given to the subject since the previous study visit and the amount of study drug returned.
- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

Once a representative from the Sponsor is able to confirm drug accountability for a completed subject, unused study drug and nebulizers will be returned to a Sponsor designated location for destruction.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with ICH and GCP guidelines and all applicable national regulations. The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the sponsor for submission to those regulatory authorities and IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/EC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/EC-approved informed consent form prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject and the original will be retained in the study site's records.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/EC and provide the sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's informed consent form and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the informed consent form and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/EC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the informed consent form, the Investigator is responsible for obtaining IRB/EC approval of these amended documents prior to implementation. Copies of the IRB/EC correspondence and approval letters must be sent to the Sponsor.

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/ECs that require it.

A written summary of the study will be provided by the Investigator to the IRB/EC following study completion or termination according to the IRB or EC standard procedures. Additional updates will also be provided in accordance with the IRB/EC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical trial, at a minimum, the following documents will be provided to the site: Investigators' Brochure, Protocol, Informed Consent Form, Subject Dosing Diary, the Tyvaso Inhalation System IFU, Budget Agreement, and Case Report Form.

At a minimum, the site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/EC Composition and Roster, IRB/EC protocol and informed consent approval letters, and Curriculum Vitae of study staff listed on the 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, the FDA or other regulatory bodies, and the IRB/EC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/EC or the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects and any report published will not identify the subject's name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially adversely affect the safety of participating subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria may be made only after consultation between United Therapeutics Corporation or its designee and the Investigator.

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/EC prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/EC for each study site.

At the end of the study, where applicable, a final report will be provided to the local regulatory agencies.

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must

notify United Therapeutics Corporation before any disposal or change in location of study records.

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH, and GCP guidelines, monitors for United Therapeutics Corporation or its designee will periodically contact the site and conduct on-site visits. During these visits, the monitor will at a minimum: confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the monitor to discuss any findings or any relevant issues.

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15 APPENDICES

15.1 PROCEDURE FOR SIX-MINUTE WALK TEST

General Procedures

The 6MWT should be administered by the same tester at each study site throughout the study, whenever possible. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines[1,2] and the usual practice of the investigative site. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate by simple face mask at all subsequent 6MWT assessments.

The area used for the 6MWT should be pre-measured at approximately 30 meters in length and at least 2 to 3 meters in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested but the clock will continue to run. At the end of 6 minutes, the tester will call "stop where you are" while simultaneously stopping the watch and then measure the distance walked.

Instructions to the Subject

Subjects will be instructed that the preceding meal should be light. Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following **exact** dialogue with the subject:

"The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (e.g., chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the six-minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"

"Start when I say "GO."

The person administering the test will tell the subject the time at each minute by saying:

"You have 5 minutes to go."

"You have 4 minutes to go."

"You have 3 minutes to go."

"You have 2 minutes to go."

"You have 1 minute to go."

At 6 minutes, the person administering the test will tell the subject: "stop where you are."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

[1] ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002; 166: 111–117.
[2] Holland, A. E., M. A. Spruit, T. Troosters, M. A. Puhan, V. Pepin, D. Saey, M. C. McCormack, B. W. Carlin, F. C. Sciurba, F. Pitta, J. Wanger, N. MacIntyre, D. A. Kaminsky, B. H. Culver, S. M. Revill, N. A. Hernandes, V. Andrianopoulos, C. A. Camillo, K. E. Mitchell, A. L. Lee, C. J. Hill and S. J. Singh (2014). "An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease." Eur Respir J 44(6): 1428-1446.

15.2 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Investigator or a designated member of his/her staff will probe each subject for any AEs that may have occurred. The Investigator should always ask the same question when conducting the verbal probe in order to ensure uniformity between subjects. The Investigator should ask:

"How are you doing (feeling)?"

Based on the subject's response to this question, the Investigator should ask additional questions relevant to the specific complaint such as:

"How severe is/was the symptom?"

"How often did the symptom occur?"

"How long did the symptom last?"

It is the Investigator's responsibility to review the results of all diagnostic and laboratory tests as they become available and ascertain if there is a clinically significant change from Baseline. If the results are determined to be a clinically significant change from Baseline, this should be reported as an AE. The Investigator may repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the abnormality should be used as the reported AE.

Using provided definitions, the Investigator will then:

(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

Definitions of Intensity, Seriousness, Causality, Action Taken, and Outcome

INTENSITY

An assessment of the relative intensity (severity) of an AE is based on the Investigator's clinical judgment. The maximum intensity encountered during the evaluation period should be checked. The assessment of intensity should be independent of the assessment of the seriousness of the AE.

SERIOUSNESS

A serious AE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization*, is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

*Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (e.g., hospitalization for a routine RHC).

- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (e.g., pre-planned operation which does not lead to further complications etc.).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

An estimate of causality between a specified AE and the study drug is made by the Investigator. Several factors should be considered when determining causality. These factors include temporal relationship and response to withdrawal or reintroduction of the study drug.

Definitions of the causality categories are as follows:

- NOT RELATED – There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE, or any of the following:
    - An event that precedes the first administration of study drug
    - An event for which the cause is clearly related to an external event
    - Temporal relationship to study drug is atypical
    - Is readily explained by an intercurrent illness AND has an expected level of severity, duration and resolution
    - An alternative explanation (concomitant drug, intercurrent illness) is likely
- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:
    - Has a reasonable temporal relationship to study drug
    - The event has a plausible biological link to the activity of the study drug
    - Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration or complication
- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge - the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
    - Has a reasonable temporal relationship to study drug
    - The event has a plausible biologic link to the activity of the study drug
    - Not readily explained by an intercurrent illness
    - Not readily explained by external event
    - Improves on discontinuation of study drug
    - If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose or regimen of the study drug was not changed.
- Dose Increased – The dose or regimen of study drug was increased
- Dose Decreased – The dose or regimen of study drug was decreased
- Drug Interrupted – Administration of the study drug was stopped temporarily
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted
- Unknown – Changes to the administration of the study drug cannot be determined
- Not Applicable

*NOTE: Only the last study drug action should be recorded in the eCRF. For example, if the study drug is withdrawn and then the decision is made to restart, the dose modification of "Drug interrupted" should be reported on the SAE form.

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.
- Recovered/Resolved with Sequelae – The AE is considered resolved however there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.
- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the AE cannot be determined.

15.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

	Very good	Good	Fair	Poor	Very poor
Please check one box to show how you describe your current health:	☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:

- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

The most important problem I have ☐
Causes me quite a lot of problems ☐
Causes me a few problems ☐
Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

My respiratory problems made me stop working altogether ☐
My respiratory problems interfere with my job or made me change my job ☐
My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath these days.

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you these days.

For each statement, please check (✓) ***the box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

For each statement, please check (✓) ***the box*** that applies to you ***these days:***

	True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems usually affect your daily life.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

....

....

....

....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Final Protocol - RIN-PH-201

Amendment 3

15February2017

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

IND 70,362

Protocol RIN-PH-201

CONFIDENTIAL

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	21 October 2015
Amendment 1	20 November 2015
Amendment 2	13 September 2016
Amendment 3	15 February 2017

LIST OF CONTACTS FOR STUDY

Study Sponsor	United Therapeutics Corp. 55 TW Alexander Drive Research Triangle Park, NC 27709
	[redacted]
	[redacted]
	[redacted]
	[redacted]
[redacted]	[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease," protocol amendment 3 dated 15 February 2017 and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56, and 312 and any local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of United Therapeutics Corp.

I also have read the current Investigator's Brochure for inhaled treprostinil and acknowledge that review of the information contained in the Investigator's Brochure is a requirement for Investigators before using inhaled treprostinil in a clinical study.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and Ethics Committee/Institutional Review Board approval documents have been obtained.

_______________________________ _______________________________
Signature of Principal Investigator Date

_______________________________ _______________________________
Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Title	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease
Study Phase	Phase II/III
Indication	Pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE)
Primary Objective	To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE
Primary Endpoint	To evaluate the change in 6-minute walk distance (6MWD) measured at peak exposure from Baseline to Week 16
Secondary Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD from Baseline to Week 12 2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16 3. Change in trough 6MWD from Baseline to Week 15
Exploratory Endpoints	To evaluate the effect of inhaled treprostinil on the following parameters: 1. Change in peak 6MWD from Baseline to Week 4 2. Change in peak 6MWD from Baseline to Week 8 3. Change in quality of life (QOL) as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16 4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met: a. Hospitalization due to a cardiopulmonary indication

	b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart c. Death (all causes) d. Lung transplantation 5. Change in distance saturation product (DSP) from Baseline to Week 16 6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16 7. Optional evaluation of whole genome sequence at Baseline
Safety Endpoints	1. Adverse events (AEs) 2. Oxygenation a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO_2]) b. Supplemental oxygen requirement (L/min) 3. Pulmonary function: a. Forced expiratory volume in 1 second (FEV1) b. Forced vital capacity (FVC) c. Total lung capacity (TLC) d. Lung diffusion capacity (DLCO) 4. Clinical laboratory parameters 5. Vital signs 6. Electrocardiograms (ECG) 7. Hospitalization due to a cardiopulmonary indication 8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Study Design	Multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study
Sample Size	Approximately 314 subjects at approximately 120 centers

Summary of Subject Eligibility Criteria	Inclusion criteria:
	1. Subject voluntarily gives informed consent to participate in the study.
	2. Males and females aged 18 years or older at the time of informed consent.
	  a. Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will:
	    i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
	    ii. Use 2 medically acceptable, highly-effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug.
	  b. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
	3. The subject has a confirmed diagnosis of World Health Organization (WHO) Group 3 PH based on computed tomography (CT) imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomization. Subjects may have any form of ILD or CPFE.
	4. Subjects are required to have a right heart catheterization (RHC) within 1 year prior to randomization with the following documented parameters:
	  a. Pulmonary vascular resistance (PVR) > 3 Wood Units (WU) and
	  b. A pulmonary capillary wedge pressure (PCWP) of $\leq$ 15 mmHg and
	  c. A mean pulmonary arterial pressure (mPAP) of $\geq$ 25 mmHg
	5. Baseline 6MWD $\geq$ 100 meters

6. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization.
7. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.
8. Subjects with connective tissue disease (CTD) must have a Baseline FVC of < 70%.

Exclusion criteria:

1. The subject has a diagnosis of pulmonary arterial hypertension (PAH) or PH for reasons other than WHO Group 3 PH-ILD as outlined in inclusion criterion 3.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.
3. The subject has received any PAH approved therapy including: prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE5-I), or soluble guanylate cyclase (sGC) stimulator within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
   a. PCWP > 15 mmHg
   b. Left ventricular ejection fraction < 40%.

   Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) will not be excluded.
5. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.

	6. Current use of any inhaled tobacco/marijuana products or a significant history of drug abuse at the time of informed consent. 7. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization. 8. Initiation of pulmonary rehabilitation within 12 weeks prior to randomization. 9. In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity) that would likely be the primary limit to ambulation (as opposed to PH). 10. Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomization. 11. Severe concomitant illness limiting life expectancy (< 6 months). 12. Acute pulmonary embolism within 90 days of randomization.
Drug Dosage and Formulation	Inhaled treprostinil (6 mcg/breath) or placebo Treatment Phase: All subjects will initiate inhaled treprostinil or placebo at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated.
Control Group	Placebo
Route of Administration	Inhaled

Procedures	Subjects will be assessed during Screening and Baseline to determine eligibility for the study. Once eligible, 5 Treatment Phase visits to the clinic will be required at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit). An Early Termination (ET) Visit will be conducted for subjects who end treatment prior to Week 16; all assessments planned for the final Week 16 Visit will be conducted during the ET Visit, as applicable. Subjects will also be contacted at least weekly by telephone or email to assess tolerance to study drug, AEs, and changes to concomitant medications. Key Assessments: • Pregnancy test: Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit or ET. • Blood for NT-proBNP and clinical labs will be obtained at Baseline, Week 8, and Week 16 or ET. • A peak 6-minute walk test (6MWT) will be conducted at Baseline, Week 4, Week 8, Week 12, and Week 16 or ET. • A trough 6MWT will be performed at Week 15 (at least 24 hours prior to the Week 16 6MWT). • Pulse oximetry will be performed immediately prior to, during, and immediately after each 6MWT. • Pulmonary function tests (PFTs) will be conducted at Baseline, Week 8, and Week 16 or ET. • SGRQ will be completed at Baseline and Week 16 or ET. • An optional blood sample will be collected for whole genome sequencing at Baseline. • An optional blood sample will be collected for the analysis of biomarkers (specific targets to be determined) at Baseline and Week 16 or ET. • An ECG will be conducted at Baseline and Week 16 or ET. • Hospitalizations due to cardiopulmonary indications and exacerbations of underlying lung disease will be evaluated from the time of informed consent until study discontinuation.

	• Time to clinical worsening will be evaluated from the time of randomization until study discontinuation.
Statistical Considerations	Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD measured at peak exposure assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%. The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. The clinical hypothesis is that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between 2 treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.
Sponsor	United Therapeutics Corp. 55 TW Alexander Drive P.O. Box 14186 Research Triangle Park, NC 27709 United States of America

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1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary hypertension (PH) is defined as an elevation in pulmonary arterial pressure and pulmonary vascular resistance (PVR). The World Health Organization (WHO) classifies PH due to lung diseases and/or hypoxemia as WHO Group 3 PH (Simonneau 2009). This classification includes PH due to interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).

Interstitial lung disease encompasses a heterogeneous group of parenchymal lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs within the lungs (Travis 2013, Seeger 2013). Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs. The symptomatology of ILD is non-specific, and covers a wide range of symptoms, whose severity can vary substantially among patients. The incidence of PH in ILD has been reported in up to 86% of patients and is associated with a poorer prognosis and decreased quality of life (QOL) (Nathan 2008, Nathan 2013).

Combined pulmonary fibrosis and emphysema is characterized by emphysema, fibrosis, and abnormalities of gas exchange (Jankowich 2012). Up to 50% of CPFE patients have been reported to develop PH with increased PVR associated with a decreased survival (Cottin 2010, Seeger 2013).

There are no approved treatments for PH in patients with ILD or CPFE; however, the results of some approved therapies for pulmonary arterial hypertension (PAH) have stimulated further investigation in these indications (Seeger 2013, Saggar 2014, Agarwal 2015, Roccia 2013).

1.2 INHALED TREPROSTINIL BACKGROUND

1.2.1 General Pharmacology

Treprostinil, 2-[[(1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid, is a chemically stable tricyclic analogue of prostacyclin. The pharmacology of treprostinil is well-characterized and approved for the

treatment of PAH following either the subcutaneous (SC), intravenous (IV), inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration.

Prostacyclin is known to lower pulmonary artery pressure, increase cardiac output without affecting the heart rate (HR), improve systemic oxygen transport and possibly reverse pulmonary arterial remodeling. There is increasing evidence that the ability to block the proliferation of pulmonary artery smooth muscle cells, along with vasodilation, may contribute to the therapeutic effects of prostacyclin in the treatment of PAH. Treprostinil acts by triggering direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In vitro, treprostinil induced concentration dependent relaxation of rabbit isolated pre-contracted mesenteric arteries and inhibited adenosine diphosphate induced platelet aggregation in human and rat platelet rich plasma. In animals, the vasodilatory effects of treprostinil reduce right and left ventricular afterload, thereby increasing cardiac output and stroke volume. The mechanism of action of treprostinil is therefore likely to be multifactorial.

Treprostinil for inhalation (Tyvaso®) is approved in the United States, Argentina, and Israel for the treatment of PAH (WHO Group 1) in patients with New York Heart Association (NYHA) Functional Classification III symptoms, to increase exercise ability.

1.2.2 General Toxicology

A well-defined clinical safety profile exists for treprostinil sodium; acute toxicity studies, repeat-dose toxicity studies, reproductive toxicity studies, and genotoxicity studies have been performed in both rats and dogs and support the chronic administration to patients (Remodulin® Package Insert 2014).

The toxicokinetic profile of treprostinil was also evaluated in acute and repeat dose toxicity studies of up to 13 weeks in duration in rodents and dogs which supported the chronic administration of inhaled treprostinil to patients. In addition, a 2-year rat carcinogenicity study was performed with treprostinil inhalation at target doses up to 5.26, 10.6, and 34.1 mcg/kg/day which found no evidence for carcinogenic potential associated with inhaled treprostinil in rats at systemic exposure levels up to 35 times the clinical exposure at the target

maintenance dose of 54 mcg. Refer to the inhaled treprostinil Investigator's Brochure for a full description of nonclinical data.

1.2.3 Clinical Experience

A series of acute and chronic investigator-initiated clinical studies were conducted with inhaled treprostinil to optimize the formulation for inhalation, determine dose response, tolerability, and safety and also to evaluate safety and tolerability when combined with other PAH therapies (Channick 2006, Voswinckel 2006). In the acute dosing studies, administration of inhaled treprostinil resulted in pulmonary vasodilation at relatively low doses. In the chronic studies, administration of inhaled treprostinil resulted in sustained improvement of exercise capacity.

A randomized, double blind, placebo controlled, Phase III study (TRIUMPH-I) was conducted to assess the safety and efficacy of inhaled treprostinil in combination with approved PAH therapies. Two hundred and thirty-five subjects who were clinically stable on an approved background oral PAH therapy (bosentan or sildenafil) were randomly allocated to receive either placebo or inhaled treprostinil for 12 weeks. The primary efficacy endpoint was change in exercise capacity at Week 12 as measured by 6-minute walk distance (6MWD). At Week 12, subjects receiving inhaled treprostinil had a median improvement of +21.6 meters in 6MWD and subjects in the placebo group had a median improvement of +3.0 meters. The Hodges-Lehmann placebo-corrected median change from baseline in peak 6MWD was +20.0 meters ($p=0.00044$). The durability of this result was supported by secondary measures related to the trough 6MWD, which was measured at least 4 hours after the last dose of inhaled treprostinil. At Week 12, trough 6MWD showed a placebo-corrected median treatment effect of 13.7 meters ($p=0.0066$). The most commonly reported adverse events (AEs) in the inhaled treprostinil group were cough (54%), headache (41%), and nausea (19%). There were no remarkable treatment-related changes in vital signs, physical examination (PE) findings, chest x-rays, pulmonary function tests (PFTs), or clinical laboratory parameters (McLaughlin 2010).

An open-label, extension study of the TRIUMPH-I study to evaluate the use of long-term inhaled treprostinil therapy was also conducted (TRIUMPH-OL). Subjects received 1 to

12 breaths (6 to 72 mcg) 4 times daily to achieve daily doses of 24 to 288 mcg. The longest duration of inhaled treprostinil exposure in the open-label study was 5.4 years and the mean duration 2.3 years. There were observed improvements in median 6MWD at 6, 12, 18, and 24 months of 28, 31, 32, and 18 meters, respectively. These data support the durability of improvement in 6MWD obtained with inhaled treprostinil as demonstrated during the double-blind phase of the study. Therapeutic benefit was also noted with improvements in the Borg dyspnea score, NYHA Functional Classification, and QOL. Survival was robust with 1 and 2 year Kaplan-Meier survival estimates of 97% and 91%, respectively, for subjects that remained in the study. The most frequently reported AEs during the open-label study were cough (39%), headache (31%), upper respiratory tract infection (22%), and nausea (22%). There were no clinically significant changes in clinical chemistry or hematology parameters. Unique findings that related to the inhaled route of administration, in addition to cough, were throat pain and throat irritation, occurring in 12% and 10% of subjects, respectively. These events were usually of mild or moderate severity and transient in duration. In a few subjects, these specific AEs were more pronounced as 6 subjects (3%) discontinued inhaled treprostinil due to cough, including 1 subject (<1%) with dry throat (Benza 2011).

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

Inhaled treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in patients with WHO Group 1 PH (McLaughlin 2010). Inhaled treprostinil is expected to directly target the more ventilated portion of the lungs in patients with WHO Group 3 PH minimizing the risk of ventilation perfusion mismatch and allowing for improvements in exercise capacity (Seeger 2013).

The use of inhaled prostacyclin therapy in patients with WHO Group 3 PH has been recently evaluated. In particular, Wang and colleagues (Wang 2015) reported data on 67 chronic obstructive pulmonary disease (COPD) patients with PH and found no change in arterial blood gases when a single dose of iloprost was administered during right heart catheterization (RHC). In addition, Bajwa and colleagues recently completed a prospective 16-Week study in 9 COPD subjects with PH which reported no notable changes in arterial blood gases over the 16-Week treatment period (Bajwa 2016). Finally, Agarwal and colleagues (Agarwal

2015) recently presented data on 35 patients with WHO Group 3 PH who received treatment with inhaled treprostinil for 6 months. This retrospective review reported a mean increase from baseline in 6MWD of 61 meters with obstructive and restrictive patients reporting mean increases of 71 meters and 50 meters, respectively. Notably, this study also found that inhaled treprostinil was well tolerated with cough being the most commonly reported AE. Data from these recently completed pilot studies suggest that inhaled treprostinil can be safely administered in patients with WHO Group 3 PH.

1.4 CLINICAL HYPOTHESIS

This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects with PH associated with ILD including CPFE.

2 OBJECTIVES

To evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE.

2.1 PRIMARY ENDPOINT

To evaluate the change in 6MWD measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD from Baseline to Week 8
3. Change in QOL as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Time to clinical worsening from the time of randomization until 1 of the following criteria are met:

   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
5. Change in distance saturation product (DSP) from Baseline to Week 16
6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16
7. Optional evaluation of whole genome sequence at Baseline

2.4 SAFETY ENDPOINTS

To evaluate the effect of inhaled treprostinil on the following parameters:

1. AEs
2. Oxygenation
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO2])
   b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
   a. Forced expiratory volume in 1 second (FEV1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalization due to a cardiopulmonary indication
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study. Subject eligibility will be based on inclusion and exclusion criteria described in Section 4. Approximately 314 eligible subjects will be randomized to study treatment in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤ 350 meters and > 350 meters). Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo screening assessments as described in Sections 7.1 and 7.3. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6-minute walk test (6MWT) used to confirm eligibility criteria must be performed prior to randomization.

Baseline Visit: The Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments (Sections 7.2 and 7.3), be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6MWT used to confirm eligibility criteria must be performed prior to randomization.

Treatment Phase: The Treatment Phase consists of 5 study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit; at least 24 hours after the Week 15 Visit). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

A schedule of visits and assessments is presented in Section 3.2.

3.2 OVERALL SCHEDULE OF TIMES AND EVENTS

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
Study Day	**-30 to -1**	**1**	**1**	**29**	**57**	**85**	**106**	**113**	
Informed Consent	X		X						
Subject Eligibility[c]	X	X	X						
Pre-Baseline Review Form[c]	X		X						
Medical History with PH History and Demographics	X		X						
SGRQ		X	X					X	X
Physical Examination	X		X					X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments	X	X	X		X			X	X
NT-proBNP[e]		X	X		X			X	X
Blood Sample for Biomarker Evaluation (Optional)[f]		X	X					X	X
Blood Sample for Whole Genome Sequencing (Optional)[g]		X	X						
Urine Pregnancy Test[h]	X	X	X	X	X	X	X	X	X

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
12-Lead ECG		X	X					X	X
6MWT[i]	X	X	X	X	X	X		X	X
Trough 6MWT[j]							X		
Pulse Oximetry[k]	X	X	X	X	X	X	X	X	X
Documentation of Supplemental Oxygen Requirement	X	X	X	X	X	X	X	X	X
PFTs[l]		X	X		X			X	X
Randomization		X	X						
Device Training		X	X						
Dosing instructions / Dosing / Dosing Diary / Accountability		X[r]	X[r]	X	X	X	X	X	X
Weekly Telephone / Email Contact[m]		X--	X--	--X--	--X--	--X--	--X--	--X	
Adverse Events[n]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Concomitant Medications	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Hospitalization due to a cardiopulmonary indication[o]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X
Exacerbations of Underlying Lung Disease[p]	X--	--X--	--X--	--X--	--X--	--X--	--X	--X	X

Study Procedures	Screening Phase[a]	Baseline[a]	Combined Screening & Baseline Visit[a]	Treatment Phase					
Study Week				Week 4[b]	Week 8[b]	Week 12[b]	Week 15[b,s] (Trough 6MWD)	Week 16[b] (at least 24 hours after Week 15)	Premature Discontinuation of Study Drug / Early Study Termination[s,t]
Time to Clinical Worsening[q]		X--	--X--	--X--	--X--	--X--	--X--	--X	X

Abbreviations: ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFTs, pulmonary function tests; PH, pulmonary hypertension; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; CT, computed topography; SpO_2, saturation of peripheral capillary oxygenation; HR, heart rate; eCRF, electronic case report form; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, lung diffusion capacity; AE, adverse event; SAE, serious adverse event; 6MWD, 6-minute walk distance; ET, early termination

[a] Screening Visit assessments can occur up to 30 days prior to the first dose of study drug. Baseline assessments can occur up to 48 hours prior to the first dose of study drug to allow for scheduling of all activities; however, the Baseline 6MWT must be performed prior to randomization. Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs, 6MWT, and CT scan (if a historical scan within 6 months is not available) assessments used to determine eligibility criteria must be performed prior to randomization. Sites should provide a completed Pre-Baseline review form to the Medical Monitor which will be reviewed, signed, and returned to the site prior to randomization.

[b] The visit window for Week 4, Week 8, Week 12, Week 15, and Week 16 is ± 5 days. The Week 16 visit must occur at least 24 hours after the Week 15 visit.

[c] For the Screening and Baseline Visits, the subject must be evaluated for and meet all inclusion/exclusion criteria.

[d] Vital signs must be collected after 5 minutes of rest (seated); no other measurements or procedures should be performed during this 5-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT then they should be obtained after recovery from the 6MWT.

[e] Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT and will occur prior to randomization at Baseline (or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined).

[f] For subjects consenting to the optional biomarker sample.

[g] For subjects consenting to the optional whole genome sequencing sample.

[h] For females of childbearing potential.

[i] If the subject has not previously undergone a 6MWT at the study site on the course intended for use during the study, a practice test must be conducted at the Screening Visit and must precede the Baseline 6MWT by at least 1 day. The Baseline 6MWT must precede randomization. The Week 4, Week 8, Week 12, and Week 16 peak 6MWT must occur within 10 to 60 minutes after the most recent study drug dose. Prior to the start of each 6MWT the subject should rest (seated) for at least 10 minutes. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[j] The Week 15 trough 6MWT must occur at least 4 hours after the most recent study drug dose and at least 24 hours prior to the Week 16 6MWT. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. The supplemental oxygen flow rate must be recorded at each study visit, as applicable.

[k] Pulse oximetry will be performed immediately prior to, during, and immediately following each 6MWT. Pulse oximetry will include the measurement of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the eCRF. In addition, the lowest recorded SpO_2 obtained during each 6MWT will be recorded in the eCRF.

[l] PFTs will include the evaluation of FEV1, FVC, TLC, and DLCO. Baseline PFTs must be performed prior to randomization. PFTs should be performed after recovering from the Baseline, Week 8, and Week 16 or ET 6MWTs.

[m] At least weekly telephone contact is required throughout the study (may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). Subjects may be contacted via email in lieu of a telephone call. A copy of the emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by phone or in clinic for clinically significant AEs or other emergent issues.

[n] All AEs will be documented from the time of informed consent until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed and should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit (Week 16).

[o] Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration, should also be recorded as SAEs per Appendix 15.2.

[p] Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (see Section 3.3.2.10). Exacerbations will also be recorded as AEs or SAEs per Appendix 15.2.

[q] Time to clinical worsening will be measured from the time of randomization until 1 of the following criteria are met: hospitalization due to a cardiopulmonary indication; decrease in 6MWD > 15% from Baseline directly related to the disease under study, at 2 consecutive visits and at least 24 hours apart; death (all causes); or lung transplantation.

[r] Once all entry criteria have been met and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (Defined as Day 1).

[s] Subjects who permanently discontinue study drug during the 16-week Treatment Phase are encouraged to undergo premature termination assessments prior to discontinuing study drug and are required complete all remaining scheduled study visits through Week 16 (excluding the Week 15 Visit) to be eligible for entry into the open-label study.

[t] The premature termination of study drug visit should be conducted prior to study drug discontinuation or as close as possible to the last dose of study drug.

3.3 CLINICAL ASSESSMENTS

3.3.1 Efficacy

3.3.1.1 6-Minute Walk Test

The 6MWT is a validated and reliable measure of exercise capacity in patients with chronic respiratory diseases (Holland 2014). This study will utilize an unencouraged 6MWT to minimize potential bias associated with encouragement. All 6MWTs will be conducted by qualified, trained personnel in a designated 6MWT area which meets the requirements as described in Appendix 15.1. Prior to the start of each 6MWT the subject must rest (seated) for at least 10 minutes. This 6MWT protocol applies to the practice (if applicable), Baseline, and treatment 6MWTs. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments. Pulmonary rehabilitation may not be introduced to a subject's treatment regimen between randomization and Week 16 or until the permanent discontinuation of study drug. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.1 Practice 6-Minute Walk Test

All subjects must have a documented 6MWT conducted at the study site on the course intended for use during the study. Subjects who have not previously performed the 6MWT at the study site on the course intended for use during the study, must perform a practice 6MWT at the study site at least 1 day prior to the Baseline Visit.

3.3.1.1.2 Baseline 6-Minute Walk Test

The Baseline 6MWT must be performed prior to randomization. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

Note: The Baseline 6MWT (not the practice 6MWT) will determine the subject's eligibility to participate in the study (6MWD $\geq$ 100 meters per inclusion criteria).

3.3.1.1.3 Treatment 6-Minute Walk Tests

3.3.1.1.3.1 Peak 6-Minute Walk Tests

Peak 6MWTs will be conducted at Weeks 4, 8, 12, and 16 or Early Termination (ET). The 6MWT must be conducted between 10 to 60 minutes after the most recent dose of study drug. If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate at all subsequent 6MWT assessments. The Week 16 peak 6MWT should occur at least 24 hours after the Week 15 Visit. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

3.3.1.1.3.2 Trough 6-Minute Walk Test

A trough 6MWT will be performed during the Week 15 Visit. The trough 6MWT must be performed at least 4 hours after the most recent dose of study drug and at least 24 hours prior to the Week 16 6MWT. If subjects are receiving supplemental oxygen during the Baseline 6MWT, they must continue to receive the same flow rate at all subsequent 6MWT assessments. Refer to Appendix 15.1 for guidelines regarding the 6MWT assessment. Pulse oximetry is to be performed immediately prior to, during, and immediately following each scheduled 6MWT as outlined in Section 3.3.2.6.1.

Subjects who discontinue study drug prematurely prior to the Week 15 Visit do not need to return to the clinic for the Week 15 Visit to be eligible for participation in the open-label extension study (Section 7.8).

3.3.1.2 St. George's Respiratory Questionnaire

The SGRQ will be conducted at Baseline (prior to study drug) or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined and at Week 16 (or ET for those subjects discontinuing study drug/study prematurely). The SGRQ should be completed as the first assessment during these visits (after informed consent is obtained) before the subject completes any of the other scheduled visit assessments. A copy of the SGRQ can be found in Appendix 15.3.

3.3.1.3 N-terminal Pro-brain Natriuretic Peptide

Plasma NT-proBNP concentration is a useful biomarker associated with changes in right heart morphology and function (Fijalkowska 2006). NT-proBNP sample collection will occur at Baseline (or as part of the Screening Visit assessment if the Screening and Baseline Visits are combined) prior to starting study drug, Week 8, and Week 16 or ET. Blood for NT-proBNP assessment must be drawn prior to conducting the 6MWT.

3.3.1.4 Time to Clinical Worsening

Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:

a. Hospitalization due to a cardiopulmonary indication
b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
c. Death (all causes)
d. Lung transplantation

Because there are no Food and Drug Administration (FDA) approved therapies for the treatment of WHO Group 3 PH, subjects experiencing clinical worsening may remain on study therapy for the duration of the study (or until criteria for study termination are met per Section 8.1 of the protocol). However, if a subject is removed from study therapy due to clinical worsening, the subject must return to the clinic for regularly scheduled study visits (excluding the Week 15 Visit) to be eligible for the open-label extension study (Section 7.8). Subjects experiencing death or lung transplantation will be discontinued from the study per Section 8.1 of the protocol.

3.3.1.5 Change in Distance Saturation Product

Change in DSP is the product of distance walked and lowest SpO_2 recorded during the 6MWT. This assessment has been shown to be predictive of mortality in patients with idiopathic pulmonary fibrosis and as such will be evaluated as an exploratory endpoint in this study (Lettieri 2006). Change from Baseline to Week 16 or ET in DSP will be calculated.

3.3.1.6 Optional Biomarker

For subjects consenting to the optional biomarker sample, blood will be collected for the evaluation of biomarkers (specific targets to be determined) at Baseline and at Week 16 or ET.

3.3.1.7 Optional Whole Genome Sequencing

For subjects consenting to whole genome sequence analysis, a blood sample will be collected at Baseline. These samples will be shipped to the central laboratory for processing and storage prior to analysis. Whole genome sequences will be analyzed for genetic makers that may be associated with clinical response and tolerability.

3.3.2 Safety

During this study, treatment emergent changes in PE findings, vital signs, clinical laboratory parameters, ECG parameters, PFTs, oxygenation, and the development of AEs after treatment will be the primary assessments of safety. Hospitalizations due to cardiopulmonary indications will also be recorded from the time of informed consent until study termination (or ET for those subjects discontinuing the study prematurely). Exacerbations of underlying lung disease will also be recorded from the time of informed consent until study termination.

3.3.2.1 Medical History and Physical Examinations

A complete medical history, demographics, PH history, and PE will be conducted during Screening. If any changes to the medical history occur between the Screening and Baseline Visit, those should be recorded. Significant past or present illnesses, current prescription or nonprescription medications (including vitamins and herbal products), and history of allergies or idiosyncratic responses to drugs should be recorded. Any significant changes to the subject's medical condition and PE must be documented throughout the course of the study. A complete PE will also be conducted by appropriate study personnel (as documented on the Delegation of Authority Log) at the Week 16 or ET Visit. Any clinically significant changes from Baseline noted during the Week 16 or ET PE should be reported as AEs.

3.3.2.2 Vital Signs

Vital signs will be assessed at Screening, Baseline, and each subsequent study visit or ET. Vital signs measured will include blood pressure (systolic and diastolic), HR, respiratory rate

(RR), temperature, and weight. Height will be assessed at Screening only. Vital signs must be assessed following at least 5 minutes of rest (sitting) to ensure accurate measurement. No other measurements or procedures should be performed during this 5-minute period. When possible, vital signs should be collected prior to the 6MWT. If vital signs cannot be obtained prior to the 6MWT, they should be obtained after recovery of the 6MWT. Vital signs should also be assessed in the case of abnormal clinical signs and symptoms.

3.3.2.3 12-Lead Electrocardiogram

A 12-lead ECG will be recorded after at least 5 minutes of rest in the semi-recumbent position at Baseline (prior to study drug) and repeated at the Week 16 or ET Visit. Recordings should include lead II as a rhythm strip and contain at least 5 QRS complexes. ECG parameters to be collected include rhythm, HR, PR interval, QT interval, QRS duration, and any clinically significant abnormalities.

3.3.2.4 Clinical Laboratory Assessments

The results of all clinical laboratory tests conducted at Screening and Baseline must be assessed by the Investigator to determine each subject's eligibility to participate in the study prior to starting study drug. Screening and Baseline clinical laboratory assessments can be combined into a single blood draw if all eligibility criteria are met within 48 hours prior to the first dose of study drug at Baseline. Central laboratory data are ultimately used to qualify subjects for the study. However, for subjects who are well known to the Investigator and who are clinically stable, the Investigator may confirm eligibility using local laboratory values so as not to delay randomization while waiting for central laboratory results if the Screening and Baseline Visits are combined.

Clinical laboratory results outside the normal reference range must be assessed for clinical significance by the Investigator. Clinically significant refers to a laboratory value that is unusual with respect to the subject's medical history or current health status.

Clinically significant abnormal laboratory test values will be reported as AEs and treated and/or followed-up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator. Where appropriate, medical tests and examinations will be performed to assess and document resolution.

3.3.2.4.1 Clinical Chemistry and Hematology

Blood for the measurement and evaluation of clinical chemistry and hematology, will be collected at the Screening and Baseline Visits prior to administration of study drug and repeated at Week 8 and Week 16 or ET to assess for treatment-emergent changes in clinical chemistry and hematological laboratory parameters. Values for the following parameters will be obtained:

Electrolyte Panel
- Sodium
- Potassium
- Bicarbonate
- Chloride

Chemistry Panel
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Urea nitrogen
- Creatinine
- Calcium
- Albumin

Hematology Panel
- Hemoglobin
- Hematocrit
- Red blood cell count
- Red blood cell morphology
- White blood cell count
- Platelet count

3.3.2.4.2 Pregnancy Testing

Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and each subsequent study visit (or Baseline Visit if the Screening and Baseline Visits are combined) or ET. A positive pregnancy test will exclude the subject from further participation in the study. Pregnant subjects who are discontinued from the study will be transitioned to an alternate therapy at the discretion of the Investigator.

3.3.2.5 Pulmonary Function Tests

Pulmonary Function Tests will be assessed at Baseline and repeated at Week 8 and Week 16 or ET. Baseline PFTs are to be conducted prior to randomization and after recovery from the 6MWT. The Week 8 and Week 16 or ET PFTs should be conducted after recovery from the 6MWT. If the PFTs are done both prior to and after a bronchodilator, only the pre-bronchodilator values will be recorded.

The following parameters will be recorded (absolute values and % predicted): FEV1, FVC, TLC, and DLCO (uncorrected for hemoglobin and lung volume).

3.3.2.6 Oxygenation

3.3.2.6.1 Pulse Oximetry

Pulse oximetry will be assessed immediately prior to, throughout the conduct of, and immediately after each scheduled 6MWT assessment at Baseline, Week 4, Week 8, Week 12, Week 15, and Week 16 or ET. Pulse oximetry will also be performed at Screening during the practice 6MWT assessment as applicable. Pulse oximetry will include the collection of SpO_2 and HR. The SpO_2 and HR obtained immediately prior to and immediately following completion of the 6MWT will be recorded in the electronic case report form (eCRF). In addition, the lowest recorded SpO_2 obtained during each 6MWT will be recorded in the eCRF.

When possible, pulse oximetry should be recorded using the provided pulse oximeter (Nonin 3150). In the event the provided pulse oximeter cannot be used (ie, subject has known issues with obtaining accurate readings from a finger probe, etc) an alternative device may be used with prior Sponsor approval so long as the same device is used for all planned 6MWT.

3.3.2.6.2 Supplemental Oxygen Requirement

The amount of supplemental oxygen (L/min) required at rest will be assessed at Baseline and at regularly scheduled visits or ET. The amount of supplemental oxygen required at the 6MWT assessment will also be recorded for each 6MWT assessment.

3.3.2.7 Adverse Events

Adverse events will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, or until the subject is either discontinued from the study or all Week 16 study assessments have been completed. Each subject will be questioned for AEs at each scheduled study visit and during required telephone/email contacts. Subjects will also be instructed to spontaneously report all AEs throughout the study.

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final study visit. All AEs meeting the criteria for serious (ie, serious adverse events [SAEs]) should be followed until resolution, death, or the

subject is lost to follow-up even if they are ongoing more than 30 days after completion of the final study visit (Week 16 or ET). All AEs/SAEs that occur while the subject is in study will be recorded as instructed in this protocol.

Sections 9 and 15.2 provide the guidelines and definitions for recording AEs.

3.3.2.8 Concomitant Medications

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, should be recorded in the subject's source documents and captured in the eCRF as required.

3.3.2.9 Hospitalization due to Cardiopulmonary Indications

Hospitalizations due to cardiopulmonary indications must be recorded in the eCRF from the time of informed consent until study termination. Adverse events resulting in hospitalizations, regardless of cause or duration should also be recorded as SAEs per Appendix 15.2. Please note that, when possible, study medication should be continued during hospitalizations.

3.3.2.10 Exacerbations of Underlying Lung Disease

An exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality (Collard 2016). As adapted from the publication by Collard and colleagues (Collard 2016), the following diagnostic criteria may be used to help support a diagnosis of acute exacerbation:

1. Previous or concurrent diagnosis of ILD including CPFE
2. Acute worsening or development of dyspnea typically of less than 1 month duration
3. Computed topography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
4. Deterioration not fully explained by cardiac failure or fluid overload

For the purposes of this protocol, events that are clinically considered to meet the definition of acute exacerbation but fail to meet all 4 diagnostic criteria due to missing CT data should still be considered an exacerbation for reporting purposes.

Exacerbations of underlying lung disease should be recorded throughout the duration of the study from the time of informed consent until study termination. Exacerbations of underlying lung disease will also be reported as AEs or SAEs per Appendix 15.2.

3.3.2.11 Weekly Telephone/Email Contact

Weekly telephone/email contact is required throughout the 16-week study to instruct the subject to titrate their dose of study drug and to assess for AEs and concomitant medications. Weekly telephone/email contact may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit). The subject may be contacted via email in lieu of a telephone call; however, email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All telephone or email contacts (ie, any dosing instructions, AEs reported and/or medication changes) with the subject must be noted in the source documentation.

3.4 NUMBER OF SUBJECTS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

3.5 NUMBER OF CENTERS

This study is multicenter with approximately 120 participating study centers.

3.6 ESTIMATED STUDY DURATION

From Screening until study completion, expected duration of study participation is approximately 20 weeks (includes a 4-week Screening period and 16-week Treatment Phase).

4 SUBJECT ELIGIBILITY

Inclusion and exclusion criteria are to be assessed during the Screening period and reconfirmed at the Baseline Visit prior to the first dose of study drug. Study related procedures must be conducted during the Screening period after obtaining informed consent to determine subject eligibility for the study.

4.1 INCLUSION CRITERIA

1. Subject voluntarily gives informed consent to participate in the study.
2. Males and females aged 18 years or older at the time of informed consent.
   a. Females of reproductive potential[1] must be non-pregnant (as confirmed by a urine pregnancy test at screening) and non-lactating, and will:
      i. Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or
      ii. Use 2 medically acceptable, highly-effective forms of contraception[2] for the duration of study, and at least 30 days after discontinuing study drug.
   b. Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug.
3. The subject has a confirmed diagnosis of WHO Group 3 PH based on CT imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomization. Subjects may have any form of ILD or CPFE.
4. Subjects are required to have a RHC within 1 year prior to randomization with the following documented parameters:
   a. Pulmonary vascular resistance (PVR) > 3 Wood Units (WU) and
   b. A pulmonary capillary wedge pressure (PCWP) of ≤ 15 mmHg and
   c. A mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg
5. Baseline 6MWD ≥ 100 meters.
6. Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization.
7. In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits.
8. Subjects with connective tissue disease (CTD) must have a Baseline FVC of < 70%.

4.2 EXCLUSION CRITERIA

1. The subject has a diagnosis of PAH or PH for reasons other than WHO Group 3 PH-ILD as outlined in inclusion criterion 3.
2. The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy.

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[1] Females who are successfully sterilized (surgical sterilization methods include hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (defined as amenorrhea for at least 12 consecutive months) are not considered to be of reproductive potential.

[2] Medically acceptable, highly-effective forms of contraception can include approved hormonal contraceptives (oral, injectable, and implantable), and barrier methods (such as a condom or diaphragm) when used with a spermicide. For women of reproductive potential, a negative pregnancy test is required at Screening and Baseline prior to initiating study drug.

3. The subject has received any PAH approved therapy including: prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE5-I), or soluble guanylate cyclase (sGC) stimulator within 60 days of randomization.
4. The subject has evidence of clinically significant left-sided heart disease as defined by:
   a. PCWP > 15 mmHg
   b. Left ventricular ejection fraction < 40%.

Note: Subjects with abnormal left ventricular function attributable entirely to impaired left ventricular filling due to the effects of right ventricular overload (ie, right ventricular hypertrophy and/or dilatation) will not be excluded.

5. The subject is receiving > 10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline.
6. Current use of any inhaled tobacco/marijuana products or significant history of drug abuse at the time of informed consent.
7. Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization.
8. Initiation of pulmonary rehabilitation within 12 weeks prior to randomization.
9. In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity) that would likely be the primary limit to ambulation (as opposed to PH).
10. Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomization.
11. Severe concomitant illness limiting life expectancy (< 6 months).
12. Acute pulmonary embolism within 90 days of randomization.

4.3 PRESCRIBED THERAPY

Subjects must not be receiving any prostacyclin (ie, epoprostenol, treprostinil, iloprost, beraprost, or any other prostacyclin therapy) within 60 days prior to randomization (unless used for acute vasoreactivity testing) until study termination. Subjects must also not be receiving any other FDA approved PAH background therapies including: an IP receptor agonist, ERA, PDE5-I, and/or sGC stimulator within 60 days of randomization through the permanent discontinuation of study drug or study termination.

Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc) must be on a stable and optimized dose for ≥ 30 days prior to randomization. Subjects may

not newly initiate pirfenidone or nintedanib from randomization through the permanent discontinuation of study drug or study termination.

Subjects may not initiate pulmonary rehabilitation (rehab) within 12 weeks prior to randomization until the permanent discontinuation of study drug or study termination.

All concomitant medications taken during the conduct of the study, including those taken for AEs or other medical events, should be recorded in the subject's source documents and transcribed into the eCRF as required. The flow rate of supplemental oxygen should be recorded as outlined in Section 3.3.2.6.2.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo.

5.2 RANDOMIZATION

Subjects will be randomized (1:1) to receive treatment with inhaled treprostinil (6 mcg/breath) or placebo. An IXRS will be utilized for the central randomization procedure. Sites will enter values of the qualifying 6MWT and the date the test was conducted into the IXRS and will be notified if the subject qualifies for the study.

All subjects will be randomized using a centrally administered stratified permuted block randomization, stratified by Baseline 6MWD (≤ 350 meters and > 350 meters).

Prior to randomization, site personnel should complete a Pre-Baseline Review Form for review and approval by the Medical Monitor.

5.3 BLINDING

The Investigator, study site, subject and Sponsor will not be aware of the treatment allocation. All clinical study material will be provided as blinded study drug.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

Treprostinil for inhalation solution (0.6 mg/mL) is delivered via an ultrasonic nebulizer which emits a dose of approximately 6 mcg per breath. Placebo will be provided as an identical solution that will be inhaled using the same ultrasonic nebulizer. All subjects will receive study drug (inhaled treprostinil or placebo) using the commercially available TD-100 ultrasonic nebulizer (Tyvaso Inhalation System®). Subjects will be trained on inhalation of study drug using the nebulizer device. Detailed instructions for the use of these devices will be provided to all study subjects. In addition, all subjects will receive a copy of the commercially available Tyvaso Inhalation System Instructions for Use (IFU) for the TD-100 ultrasonic nebulizer.

Once informed consent has been signed, all entry criteria have been met, and the randomized treatment assignment confirmed, the first dose of study drug (3 breaths; 18 mcg) will be inhaled in the clinic, followed by at least a 1 hour observation period (defined as Day 1). Study drug doses should be maximized throughout the study, dose escalations (additional 1 breath 4 times daily) can occur up to every 3 days with a target dosing regimen of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily within 4 weeks of beginning the treatment, as clinically tolerated. Table 6-1 provides a guideline for the recommended dose escalations.

Table 6-1 Recommended Inhaled Treprostinil Dose Escalation Table

Study Day[a]	Single Dose	Total Daily Dose
Titrating to maximum dose of 12 breaths		
1-3	3 breaths QID (18 mcg)	72 mcg
4-6	4 breaths QID (24 mcg)	96 mcg
7-9	5 breaths QID (30 mcg)	120 mcg
10-12	6 breaths QID (36 mcg)	144 mcg
13-15	7 breaths QID (42 mcg)	168 mcg
16-18	8 breaths QID (48 mcg)	192 mcg
19-21	9 breaths QID (54 mcg)	216 mcg
22-24	10 breaths QID (60 mcg)	240 mcg
25-27	11 breaths QID (66 mcg)	264 mcg
28 (and beyond)	12 breaths QID (72 mcg)	288 mcg

Abbreviations: QID, 4 times daily; mcg,: micrograms
[a] Study day refers to the days on study drug with Day 1 referring to the first dose of study drug.

The dosing schedule is recommended as a guide only. The Investigator may determine the appropriate dosing schedule on an individual subject basis, considering tolerability and functional improvement.

If subjects are unable to tolerate the initial 3 breaths, they may decrease their next dose to 1 or 2 breaths of study drug (as determined by the Investigator) 4 times a day during waking hours. The subject will then gradually increase their dose to reach a minimum of 3 breaths, and titrate to a target dose of 9 breaths and a maximum dose of 12 breaths 4 times a day during waking hours, as clinically tolerated.

Dose changes should be conducted under appropriate medical supervision in consultation with the study site. Telephone calls/emails between the site and subject should occur prior to each dose adjustment or at least weekly to monitor for AEs, clinical worsening events, and make decisions about dose titration.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

During the study, the site personnel, subject, and Sponsor will remain blinded to the treatment assignment of all subjects. A medical emergency (eg, a life threatening event) constitutes the only reason for unblinding during the Treatment Phase. Appropriate communications must take place between the site and the Sponsor before accessing the IXRS to allow unblinding of a subject's treatment assignment.

6.3 COMPLIANCE

Each subject will be provided with a dosing diary in order to record dosing information from randomization until Week 16. Subjects will be required to bring the completed dosing diary and all empty and unused study drug ampoules to each scheduled study visit. At each visit, all study drug returned by the subject (used and unused) will be collected and new study drug will be dispensed. The appropriate study personnel must document the number of used and unused ampoules and determine if the appropriate amount of study drug remains based on the dose of study drug prescribed.

Subject compliance with the prescribed dosage regimen will be monitored throughout the study. At each study visit, the subject will be asked whether he or she has been compliant

with dosing instructions. If it is determined that a subject is not compliant with study drug then site personnel must re-educate the subject on proper dosing compliance and its importance. Continued non-compliance may lead to withdrawal of the subject from the study, after consultation between the Investigator and the Sponsor.

7 EXPERIMENTAL PROCEDURES

Screening may begin up to 30 days prior to first dose of study drug. Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Alternately, the Screening and Baseline assessments may be conducted in 1 visit if all assessments are performed and all entry criteria are satisfied within the 48 hours prior to randomization and first dose of study drug.

7.1 SCREENING VISIT

The recommended sequence of assessments for the Screening Visit is as follows (if not combined with the Baseline Visit [see Section 7.3 for the recommended sequence of events for the combined Screening/Baseline Visit]):

- Informed consent
- Inclusion/exclusion criteria review
    - If necessary, the following procedures may be performed during the 30 day Screening window if required to satisfy inclusion/exclusion criteria (previous medical records documenting eligibility criteria may also be used provided the previous records document subject eligibility within the protocol mandated timelines, as applicable):
        - RHC (Must be performed within 1 year prior to randomization. If a historical RHC is not available in this timeframe, a RHC may be performed during Screening so long as it is performed at least 5 days prior to randomization [Baseline (Day 1)]; a RHC cannot be combined with the Baseline Visit). Select RHC parameters will be recorded in the eCRF including: mPAP, PVR, PCWP, and vasodilator response (as applicable).
        - CT scan (must be performed within 6 months prior to randomization). A redacted copy of the CT scan used to confirm subject eligibility should be sent to the Sponsor.
        - Although not required for eligibility, the date of lung biopsy for subjects with a biopsy confirmed diagnosis of ILD will be recorded in the eCRF.
- Demographics
- PH history
- Medical history

- PE
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT, if practice 6MWT is applicable); including height, weight, RR, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature.
- Blood draws for clinical laboratory parameters
- Urine pregnancy test, for women of childbearing potential
- Practice 6MWT (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT, if applicable)
- Documentation of supplemental oxygen requirement (L/min)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Complete and submit Pre-Baseline Review Form to the Sponsor for Medical Monitor review prior to randomization

7.2 BASELINE/RANDOMIZATION VISIT

All Baseline assessments must be performed prior to the first dose of study drug. Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of assessments; however, the Baseline 6MWT must occur prior to randomization. The recommended sequence of assessments for the Baseline Visit is as follows (if not combined with the Screening Visit [see Section 7.3 for the recommended sequence of events for the combined Screening/Baseline Visit]):

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- 12-lead ECG (following at least 5 minutes of rest in the semi-recumbent position)

- Documentation of supplemental oxygen requirement (L/min)
- 6MWT (must be conducted prior to randomization; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to randomization and after recovery from the Baseline 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least 1 hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation

7.3 COMBINED SCREENING AND BASELINE

The Screening and Baseline assessments may be conducted in 1 visit if all assessments are performed and all entry criteria are satisfied within 48 hours prior to randomization and dosing of study drug. Baseline PFTs, 6MWT, and CT (if a historical assessment is not available within 6 months prior to randomization) assessments used to determine eligibility criteria may be performed on the same day but prior to randomization. The recommended order of assessments for a combined Screening and Baseline Visit is outlined below.

<u>Assessments to be completed as part of the Screening Visit</u>:

- Informed consent
- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- Inclusion/exclusion criteria review

  - RHC (Must be performed within 1 year prior to randomization. If a historical RHC is not available in this timeframe, a RHC may be performed during Screening so long as it is performed at least 5 days prior to randomization [Baseline (Day 1)]; a RHC cannot be combined with the Baseline Visit). Select RHC parameters will be recorded in the eCRF including: mPAP, PVR, and PCWP, and vasodilator response (as applicable).
  - CT scan (must be performed within 6 months prior to randomization). A redacted copy of the CT scan used to confirm subject eligibility should be sent to the Sponsor.
  - Although not required for eligibility, the date of lung biopsy for subjects with a biopsy confirmed diagnosis of ILD will be recorded in the eCRF.
- Blood draws for clinical laboratory parameters (enough blood should be drawn for local laboratory to confirm the entry criteria for hemoglobin, as well as for the complete panel for central laboratory processing)
- NT-proBNP (must be drawn prior to 6MWT and first dose of study drug; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Collection of blood sample for evaluation of whole genome sequence (optional)
- Demographics
- PH history
- Medical history
- PE
- Vital signs (following at least 5 minutes of rest; collected prior to the 6MWT or after recovery from the 6MWT); including height, weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Practice 6MWT to be conducted 1 day prior to Baseline assessments (only required if the subject has not previously performed a 6MWT at the study site; to be conducted following at least 10 minutes of rest [sitting])
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- AEs
- Concomitant medications
- Complete and submit the Pre-Baseline Review Form to the Sponsor for Medical Monitor review prior to randomization

Assessments to be completed as part of the Baseline Visit:

- Urine pregnancy test, for women of childbearing potential
- 12-Lead ECG (following at least 5 minutes of rest in the semi-recumbent position)
- 6MWT (must be conducted prior to randomization; to be conducted following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (must be done prior to randomization and after recovery from the Baseline 6MWT).
- Re-confirm inclusion/exclusion criteria (Baseline 6MWD [not the practice Screening 6MWD] will be used for inclusion/exclusion verification)
- Randomization using IXRS
- Administer study drug and provide dosing instructions and device training (subject must remain in the clinic for at least 1 hour after the first dose of study drug for observation)
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation

7.4 TREATMENT PHASE: WEEKS 4, 8, AND 12

The following assessments to be completed during the Treatment Phase:

- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters (Week 8 only)
- NT-proBNP (must be drawn prior to 6MWT; for central laboratory processing only [Week 8 only])
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (Week 8 only; to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease

- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart.
  - Death (all causes)
  - Lung transplantation
- AEs
- Concomitant medications
- Dosing instructions/study drug accountability

Please note the visit window for the Week 4, Week 8, and Week 12 Visits is ± 5 days.

7.5 TREATMENT PHASE: WEEK 15 (TROUGH)

- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- Urine pregnancy test, for women of childbearing potential
- Trough 6MWT (at least 4 hours after the last dose of study drug)
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
  - Hospitalization due to a cardiopulmonary indication
  - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  - Death (all causes)
  - Lung transplantation
- AEs
- Concomitant medications
- Dosing instructions/study drug accountability

Please note the visit window for the Week 15 Visit is ± 5 days and at least 24 hours prior to the Week 16 6MWT. If a subject discontinues study drug prematurely, the subject does not need to return to the clinic for the Week 15 Visit.

7.6 END OF STUDY (WEEK 16) AND/OR EARLY TERMINATION VISIT

The assessments to be completed during the Week 16 Visit are listed below in the recommended sequence of events. If a decision is made to early terminate a subject from study drug or from the study in its entirety, the following assessments should be conducted as soon as possible and prior to study drug discontinuation, if possible. If the subject permanently discontinues study drug prior to Week 16 for any reason, the subject should be encouraged to remain in the study and complete all visits (excluding the Week 15 Visit) up to and including Week 16:

- SGRQ (questionnaire must be administered prior to any results, procedures, or blood draws)
- PE
- Vital signs (following at least 5 minutes of rest; collected prior to 6MWT or after recovery from the 6MWT); including weight, RR, HR, SBP, DBP, and temperature.
- Documentation of supplemental oxygen requirement (L/min)
- 12-Lead ECG (following at least 5 minutes of rest in the semi-recumbent position)
- Urine pregnancy test, for women of childbearing potential
- Blood draws for clinical laboratory parameters
- NT-proBNP (must be drawn prior to 6MWT; for central laboratory processing only)
- Collection of blood sample for evaluation of biomarkers (optional)
- Peak 6MWT (must be conducted between 10 to 60 minutes after the most recent dose of study drug and following at least 10 minutes of rest [sitting])
- Pulse oximetry (to be performed immediately prior to, throughout the conduct of, and immediately following the 6MWT)
- PFTs (to be performed after recovery from the 6MWT)
- Hospitalizations due to a cardiopulmonary indication
- Exacerbations of underlying lung disease
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
    - Hospitalization due to a cardiopulmonary indication
    - Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
    - Death (all causes)
    - Lung transplantation
- AEs
- Concomitant medications
- Study drug accountability

Subjects who remain on study drug, complete all assessments during the 16-week Treatment Phase, and meet all eligibility criteria for the open-label extension study (RIN-PH-202) are eligible for an open-label extension study (RIN-PH-202). Additionally, subjects who are withdrawn from study drug prior to Week 16 due to clinical worsening should continue to return to the clinic for scheduled visits (excluding the Week 15 Visit) to be eligible for the open-label study. Refer to Section 7.8 for more information regarding access to the open-label study.

7.7 STUDY CONTACTS

During the Treatment Phase, all subjects will be contacted at least once a week via telephone or email (or more often as needed) to follow-up on adherence of the correct dose titration of study drug, and to assess for AEs and concomitant medications. A copy of emails and/or telephone contact sheets must be documented in the subject's source documentation. Email should not replace direct follow-up by telephone or in clinic for clinically significant AEs or other emergent issues. All study contacts (ie, any dosing instructions, AEs reported, and/or medication changes) with the subject will be recorded.

The weekly study contacts may be replaced by a face-to-face interaction on the weeks where study visits occur and the information can be obtained during the visit.

7.8 ACCESS TO OPEN-LABEL STUDY

Subjects who remain on study drug, complete all assessments during the 16-week Treatment Phase, and who meet all eligibility criteria for the open-label extension study (RIN-PH-202) are eligible for an open-label extension study (RIN-PH-202). Additionally, subjects who experience clinical worsening and are withdrawn from study drug prior to Week 16 should undergo premature termination assessments prior to discontinuing study drug (when possible) and complete all remaining scheduled study visits (excluding the Week 15 Visit) through Week 16 to be eligible for entry into the open-label study.

Subjects who permanently discontinue study drug during the 16-week Treatment Phase due to treatment-related AEs are not eligible for entry into the open-label study even if they complete all remaining scheduled study visits. The site personnel must never be unblinded to the treatment assignment of these subjects unless required for safety reasons.

Subjects who permanently discontinue study drug during the 16-week Treatment Phase and do not undergo premature termination assessments prior to discontinuing study drug and/or who do not complete all remaining study visits (excluding the Week 15 Visit) through the Week 16 Visit are also not eligible for entry into the open-label study. The site personnel must never be unblinded to the treatment assignment of these subjects, unless medically necessary.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

A subject may voluntarily withdraw or be withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject wishes to withdraw from further participation.
- A serious or life-threatening AE occurs or the Investigator considers that it is necessary to discontinue study drug to protect the safety of the subject.
- The subject consistently deviated from the protocol.
- Lung transplantation.
- The subject becomes pregnant.
- The subject's behavior is likely to undermine the validity of his/her results.

If a subject is discontinued from the study prematurely, the Investigator must provide an explanation in the eCRF and complete the End of Study Record for that subject. If study drug has been administered, the Investigator should make every effort to perform all scheduled evaluations prior to discharge. In the event that a subject discontinues study drug prematurely due to an AE, the subject will be followed until either the Investigator determines that the AE has resolved, it is no longer considered clinically significant, the subject is lost to further follow-up, or for 30 days if the AE extends beyond the final visit.

If a subject discontinues study drug prematurely for any reason, the subject should be encouraged to remain in the study and attend the remaining scheduled study visits (excluding the Week 15 Visit) up to and including Week 16.

8.2 LOST TO FOLLOW-UP

If a subject fails to return to clinic or respond after at least three documented attempts by the site to contact the subject by telephone or email, the Investigator should issue a written letter

by certified mail requesting the subject to contact the clinic. If no response is received, the subject will be considered lost to follow-up. The site will record the last date of contact in the eCRF as the termination date.

8.3 CRITERIA FOR TERMINATING THE STUDY

The study may be stopped at any time if, in the opinion of the Investigator and/or Sponsor, continuation of the study represents a serious medical risk to the subjects. This may include, but is not limited to, the presence of serious, life-threatening, or fatal AEs, or AEs that are unacceptable in nature, severity, or frequency. The Sponsor reserves the right to discontinue the study for any reason at any time.

8.4 CRITERIA FOR DISCONTINUING THE SITE

The study may also be terminated at a given site if:

- The Investigator elects to discontinue the study.
- The Sponsor elects to discontinue the study at the site.
- United States FDA, European, or national regulations are not observed.
- The protocol is consistently violated.
- Changes in personnel or facilities adversely affect performance of the study.

9 ADVERSE EVENT REPORTING

All AEs/SAEs that occur while the subject is participating in the study will be recorded as instructed in this protocol (Section 9.2).

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the use of the medicinal product.

An AE may include:

- An intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance.

- A worsening of an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures (eg, exacerbation of a pre-existing illness following the start of the study or an increase in frequency or intensity of a pre-existing episodic event or condition).

Thus, no causal relationship with the study drug is implied by use of the term "adverse event."

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); however, the condition for which the surgery is required may be an AE.
- Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not AEs.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- The disease or disorder being studied or a sign or symptom associated with the disease or disorder unless more severe than expected for the subject's condition.

9.1.2 Serious Adverse Event

A SAE is an AE occurring at any time after informed consent that results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Results in a medically important event of reaction

Life-threatening in this context refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent 1 of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

9.2 DOCUMENTATION OF ADVERSE EVENTS

An AE or SAE occurring during the study must be documented in the subject's source documents and on the appropriate eCRF page. Information relating to the AE such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the eCRF (see Appendix 15.2 for definitions). Where possible, AEs should be recorded using standard medical terminology. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms. If several signs or symptoms are clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome should be recorded on the eCRF page, not the individual signs and symptoms.

9.3 FOLLOW-UP OF ADVERSE EVENTS

All AEs should be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 30 days if the AE extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 4 weeks after completion of the final study visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. The eCRF pages should be updated with any new or additional information as appropriate.

9.4 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the Sponsor by fax/email (+ 1-919-313-1297 or drugsafety@unither.com) within 24 hours of awareness. A completed SAE Notification Report form along with any relevant hospital records and autopsy reports should be provided to Global Drug Safety at United Therapeutics Corporation. A follow-up SAE Notification Report form must be forwarded to Global Drug

Safety at United Therapeutics Corporation within 24 hours of the receipt of any new or updated information. The Investigator must also promptly notify their Institutional Review Board (IRB) or Ethics Committee (EC) of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

9.5 PREGNANCY

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the Sponsor within 24 hours of learning of the pregnancy by completing the Pregnancy Notification Form and submitting via fax or email to Global Drug Safety at United Therapeutics Corporation (+ 1-919-313-1297 or drugsafety@unither.com). The United Therapeutics Global Drug Safety department will follow-up with the Investigator to ensure appropriate data are provided regarding the outcome of the pregnancy, and to ask the Investigator to update the Pregnancy Notification Form. Pregnancy only becomes an AE/SAE if there is an abnormal outcome, a spontaneous abortion, an elective termination for medical reasons, or a congenital anomaly in the offspring.

9.6 SAFETY REPORTS

In accordance with national regulations, the Sponsor will notify the appropriate regulatory authority(ies), and all participating Investigators of any AE that is considered to be possibly attributable to study drug and is both serious and unexpected. The Investigator must report these AEs to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion, or study discontinuation for any reason. A representative from the Sponsor will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated and the database will be edited as appropriate. The eCRF screens are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject’s eCRF to signify his/her approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject’s

eCRF by the site after the Investigator initially signs the eCRF. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline in 6MWD assuming a standard deviation of 75 meters. The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

10.3 ANALYSIS PLAN

Details of the efficacy and safety analyses are provided below. A separate statistical analysis plan will document further details of the statistical methods to be employed, including any changes to planned analyses specified within this protocol. The analysis plan will be finalized prior to any unblinding of study data by the Sponsor. Unless otherwise specified, all statistical tests will be 2-sided at alpha level of 0.05. All statistical calculations will be completed using the latest version of SAS®.

The Intent-to-Treat (ITT) population will be defined as all subjects randomized into the study and receive at least 1 dose of study drug; all ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were actually given. All efficacy analyses will be performed on this ITT population, unless otherwise specified. The Safety population will be defined as all subjects enrolled into the study who received at least 1 dose of study drug; all Safety population subjects will be counted in the group corresponding to the study drug actually received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

10.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in 6MWD measured at peak exposure from Baseline to Week 16. This study hypothesizes that inhaled treprostinil will improve exercise capacity after 16 weeks of therapy as compared with placebo when administered to subjects

with PH associated with ILD including CPFE. Non-parametric analysis of covariance will be used to estimate the treatment effect. The magnitude of treatment effect will be estimated with the Hodges-Lehmann median difference between 2 treatment groups. For subjects who discontinue from the study early, the last observation carried forward method will be used to impute the 6MWD at Week 16.

10.3.2 Secondary Efficacy Endpoints

The effect of inhaled treprostinil will be formally tested on the following 3 secondary efficacy endpoints:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of NT-proBNP from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

The similar approach for the analysis of primary efficacy endpoint will be used. No adjustment for multiplicity is planned.

10.3.3 Exploratory Endpoints

The effect of inhaled treprostinil will be evaluated on the following parameters:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD at from Baseline to Week 8
3. Change in SGRQ from Baseline to Week 16
4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time of randomization until 1 of the following criteria are met:
   a. Hospitalization due to a cardiopulmonary indication
   b. Decrease in 6MWD > 15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
5. Change in DSP from Baseline to Week 16
6. Optional evaluation of change in biomarkers (specific targets to be determined) from Baseline to Week 16
7. Optional evaluation of whole genome sequence at Baseline

For changes in peak 6MWD and SGRQ, a similar approach for the analysis of primary efficacy endpoint will be used. For time to clinical worsening, Kaplan-Meier estimator will be provided and log-rank test will be used to compare the treatment difference.

10.3.4 Safety Analyses

The safety of inhaled treprostinil will be evaluated by comparison of the following parameters between the 2 treatment groups:

1. AEs
2. Oxygenation
   a. Pulse oximetry (SpO_2)
   b. Supplemental oxygen (L/min) requirement
3. Pulmonary function:
   a. FEV1
   b. FVC
   c. TLC
   d. DLCO
4. Clinical laboratory parameters
5. Vital signs
6. 12-Lead ECG
7. Hospitalization due to cardiopulmonary indications
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

All AEs as recorded by the Investigators will be assigned a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class by the Sponsor for reporting purposes. The summary of AEs will include the number and percentage of subjects, as well as the number of events reported for each preferred term. No inferential analyses are planned for the AEs.

Data collected prior to dosing will serve as Baseline values for the evaluation of data collected during the Treatment Phase. Summary statistics will be calculated for measured values and changes from Baseline values. Treatment-emergent changes in vital signs, ECGs, PFTs, oxygenation parameters, and clinical laboratory parameters will be summarized by treatment group. Incidence of hospitalization due to cardiopulmonary indications and exacerbations of underlying lung disease will be summarized by treatment group. No inferential analyses are planned on these safety endpoints.

10.4 INTERIM ANALYSES

Interim analyses for safety data will be performed at the request of the Data Monitoring Committee (DMC). Interim analyses for efficacy data are not planned for this study.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the clinical study report.

10.7 DATA MONITORING COMMITTEE

A DMC will be established for the study including physicians knowledgeable in the treatment of PH. Throughout the course of the study the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DMC charter. The DMC will be blinded to individual subject treatment allocation during the review process. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC charter. The Sponsor will only have access to blinded study data during this process.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

11.1.1 Study Drug

The Sponsor will supply study medication (treprostinil inhalation solution, 0.6 mg/mL or placebo), as clear liquid in 2.9 mL ampoules. The ampoules will be packaged in groups of 4, sealed in aluminum pouches. There will be 9 pouches per carton.

11.1.2 Study Device

The Sponsor will supply commercially available TD-100 nebulizers (Tyvaso Inhalation System) and accessories to the site in standard packaging labeled with the study number. The Tyvaso Inhalation System will also be provided with the commercially available IFU.

Each subject will receive 2 nebulizers at the start of the study. In addition, the subjects will be provided with a month worth of plastic accessories at each study visit.

11.2 LABELING

11.2.1 Study Drug

The foil pouch and the outer carton will each be labeled with the same information and sent to the site. At a minimum, the study medication outer packaging (pouch and carton) will be labeled to disclose clearly the product name, study number, kit identification number, expiry date, Sponsor's name and address, IFU, and storage information (subject to regulatory requirements in each study region or country).

11.2.2 Study Device

Study subjects will receive commercially available TD-100 nebulizers and accessories separately from study drug. Study subjects will receive 2 devices at Baseline supplied as a device starter kit. Subjects will receive replacement parts as part of a monthly device resupply kit. The nebulizers and accessories will be supplied using standard packaging labeled with the study number.

11.3 STORAGE AND HANDLING OF CLINICAL STUDY MATERIAL

All study drug will be stored at room temperature 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Study drug should not be frozen, refrigerated, or exposed to heat. Keep the ampoules in the foil pouch to protect from light. Once the foil pouch is opened, use within 7 days. See investigational medicinal product label for information on use and storage of the product.

Study drug will be stored in a securely locked cabinet or enclosure with appropriate temperature monitoring. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study drug to any subject not participating in this protocol.

11.4 SUPPLY AND RETURN OF CLINICAL STUDY MATERIAL

Study sites will be supplied with a sufficient quantity of study drug to begin enrollment in the study. At Baseline, an IXRS will be utilized to randomize the subjects and assign the appropriate study drug for the first 4-week treatment interval. At subsequent study visits, the IXRS will be utilized by study staff to assign subsequent study drug kits to the subjects based

upon their current treatment allocation. At each study visit, all study drug dispensed to a subject should be returned to the study site, including all used and unused ampoules.

At the end of the study, nebulizers used during the study should be collected from each subject not continuing into the open-label extension study. Subjects continuing into the open-label extension study will retain their devices for use in the open-label extension study.

11.5 DRUG ACCOUNTABILITY

The Investigator is responsible for study drug accountability and reconciliation overall and on a per subject basis. Drug accountability records are to be maintained during the study and these records include, but are not limited to: the amount of study drug received from the Sponsor, the amount dispensed to each subject, and the amount of used/unused study drug returned to the site from the subject.

At each visit, site personnel will:

- Collect and document all study drug returned by the subject (both used and unused).
- Compute study drug compliance using the dosing instructions given to the subject since the previous study visit and the amount of study drug returned.
- Re-educate the subject about the importance of following the prescribed dosing regimen (if compliance is low).

Once a representative from the Sponsor is able to confirm drug accountability for a completed subject, study drug will be returned to a Sponsor designated location for destruction and/or destroyed onsite per institutional policy. At the end of the study, nebulizers used during the study should be collected from each subject not continuing into the open-label extension study. These nebulizers will be returned to a Sponsor designated location for destruction. In the event of device malfunction, at any point during the study, the nebulizer should be returned to the Sponsor. Subjects continuing into the open-label extension study will retain their devices for use in the open-label extension study.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and all applicable national regulations.

The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to those regulatory authorities and IRBs/ECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/EC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

Before a subject is enrolled in the study, the Investigator or his/her designees must explain the purpose and nature of the study, including potential benefits and risks and all study procedures to the subject. The subject must sign and date an IRB/EC-approved ICF prior to the conduct of any study-related activities. A copy of the signed consent form will be given to the subject and the original will be retained in the study site's records.

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/EC and provide the Sponsor with a copy of the approval letter. The IRB/EC must also review and approve the study site's ICF and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/EC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the ICF, the Investigator is responsible for obtaining IRB/EC approval of these amended documents prior to implementation. Copies of the IRB/EC correspondence and approval letters must be sent to the Sponsor.

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/ECs that require it.

A written summary of the study will be provided by the Investigator to the IRB/EC following study completion or termination according to the IRB/EC's standard procedures. Additional updates will also be provided in accordance with the IRB/EC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before the commencement of the clinical study, at a minimum, the following documents will be provided to the site: Investigator's Brochure, Protocol, ICF, Subject Dosing Diary, the Tyvaso Inhalation System IFU, Clinical Trial Agreement, Budget Agreement, and eCRF.

At a minimum, the site will be required to provide the following documents to United Therapeutics Corporation or designee prior to study start: Signature page of the protocol, Form FDA 1572, Financial Disclosure Form, IRB/EC Composition and Roster, IRB/EC protocol and informed consent approval letters, and Curriculum Vitae of study staff listed on the Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

Every effort will be made to keep medical information confidential. United Therapeutics Corporation, the FDA or other regulatory bodies, and the IRB/EC governing this study may inspect the medical records of any subject involved in this study. The Investigator may release the subject's medical records to employees or agents of the Sponsor, the IRB/EC or the FDA or appropriate local regulatory agencies for purposes of checking the accuracy of the data. A number will be assigned to all subjects and any report published will not identify the subject's name.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially adversely affect the safety of participating subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria may be made only after consultation between United Therapeutics Corporation or its designee and the Investigator.

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/EC prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/EC for each study site.

At the end of the study, where applicable, a final report will be provided to the local regulatory agencies.

13.2 STUDY DOCUMENTATION AND STORAGE

In accordance with federal/national regulations, ICH, and GCP guidelines, the Investigator must retain study records for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must notify United Therapeutics Corporation before any disposal or change in location of study records.

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH, and GCP guidelines, monitors for United Therapeutics Corporation or its designee will periodically contact the site and conduct on-site visits. During these visits, the monitor will at a minimum: confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the monitor to discuss any findings or any relevant issues.

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15 APPENDICES

15.1 PROCEDURE FOR 6-MINUTE WALK TEST

General Procedures

The 6MWT should be administered by the same tester at each study site throughout the study, whenever possible. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines[1,2] and the usual practice of the investigative site. Subjects receiving supplemental oxygen during the Baseline 6MWT must continue to receive the same flow rate at all subsequent 6MWT assessments.

The area used for the 6MWT should be pre-measured at approximately 30 meters in length and at least 2 to 3 meters in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stop-watch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested but the clock will continue to run. At the end of 6 minutes, the tester will call “stop where you are” while simultaneously stopping the watch and then measure the distance walked.

Instructions to the Subject

Subjects will be instructed that the preceding meal should be light. Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following **exact** dialogue with the subject:

> “The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back

[1] ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002; 166: 111–117.
[2] Holland, A. E., M. A. Spruit, T. Troosters, M. A. Puhan, V. Pepin, D. Saey, M. C. McCormack, B. W. Carlin, F. C. Sciurba, F. Pitta, J. Wanger, N. MacIntyre, D. A. Kaminsky, B. H. Culver, S. M. Revill, N. A. Hernandes, V. Andrianopoulos, C. A. Camillo, K. E. Mitchell, A. L. Lee, C. J. Hill and S. J. Singh (2014). "An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease." Eur Respir J 44(6): 1428-1446.

and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6-minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say 'STOP,' please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"
"Start when I say 'GO.'"

The person administering the test will tell the subject the time at each minute by saying:

"You have 5 minutes to go."
"You have 4 minutes to go."
"You have 3 minutes to go."
"You have 2 minutes to go."
"You have 1 minute to go."

At 6 minutes, the person administering the test will tell the subject:

"Stop where you are."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

15.2 GUIDELINES AND DEFINITIONS FOR RECORDING ADVERSE EVENTS

The Investigator or a designated member of his/her staff will probe each subject for any AEs that may have occurred. The Investigator should always ask the same question when conducting the verbal probe in order to ensure uniformity between subjects. The Investigator should ask:

"How are you doing (feeling)?"

Based on the subject's response to this question, the Investigator should ask additional questions relevant to the specific complaint such as:

"How severe is/was the symptom?"
"How often did the symptom occur?"
"How long did the symptom last?"

It is the Investigator's responsibility to review the results of all diagnostic and laboratory tests as they become available and ascertain if there is a clinically significant change from Baseline. If the results are determined to be a clinically significant change from Baseline, this should be reported as an AE. The Investigator may repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests. When possible, a diagnosis associated with the abnormality should be used as the reported AE.

Using provided definitions, the Investigator will then:
(1) rate the intensity and seriousness of the AE, (2) estimate the causality of the AE to study drug, and (3) note actions taken to counteract the AE.

<u>Definitions of Intensity, Seriousness, Causality, Action Taken, and Outcome</u>

INTENSITY

An assessment of the relative intensity (severity) of an AE is based on the Investigator's clinical judgment. The maximum intensity encountered during the evaluation period should be checked. The assessment of intensity should be independent of the assessment of the seriousness of the AE.

SERIOUSNESS

A serious AE is one that represents an actual or potential significant hazard. This includes, but is not limited to, an event that is fatal, life-threatening, permanently or severely disabling, requires or prolongs inpatient hospitalization*, is a congenital abnormality (offspring of subject) or is medically significant (important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition).

*Hospitalizations that would not be considered SAEs include those for:

- Routine treatment or monitoring of the study indication not associated with any deterioration in condition (eg, hospitalization for a routine RHC).
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition (eg, pre-planned operation which does not lead to further complications etc).
- Treatment of an emergency, in an outpatient setting for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

CAUSALITY

An estimate of causality between a specified AE and the study drug is made by the Investigator. Several factors should be considered when determining causality. These factors include temporal relationship and response to withdrawal or reintroduction of the study drug.

Definitions of the causality categories are as follows:

- NOT RELATED – There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE, or any of the following:
  - An event that precedes the first administration of study drug
  - An event for which the cause is clearly related to an external event
  - Temporal relationship to study drug is atypical
  - Is readily explained by an intercurrent illness AND has an expected level of severity, duration, and resolution
  - An alternative explanation (concomitant drug, intercurrent illness) is likely
- POSSIBLE – There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear, study drug administration was not modified in response to the SAE, or any of the following:

- Has a reasonable temporal relationship to study drug
- The event has a plausible biological link to the activity of the study drug
- Is unlikely to be related to an intercurrent illness or has an unexpected degree of severity, duration or complication

- PROBABLE – There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge - the event resolves or improves with modification of study drug administration. Rechallenge (the original study drug was restarted) is not required, or any of the following:
  - Has a reasonable temporal relationship to study drug
  - The event has a plausible biologic link to the activity of the study drug
  - Not readily explained by an intercurrent illness
  - Not readily explained by external event
  - Improves on discontinuation of study drug
  - If study drug has been discontinued, may recur or reintroduction of study drug

ACTION TAKEN

STUDY DRUG DOSE MODIFICATION*

- Dose Not Changed – The dose or regimen of the study drug was not changed.
- Dose Increased – The dose or regimen of study drug was increased
- Dose Decreased – The dose or regimen of study drug was decreased
- Drug Interrupted – Administration of the study drug was stopped temporarily
- Drug Withdrawn – Administration of the study drug was stopped permanently and not restarted
- Unknown – Changes to the administration of the study drug cannot be determined
- Not Applicable

**NOTE: Only the last study drug action should be recorded in the eCRF. For example, if the study drug is withdrawn and then the decision is made to restart, the dose modification of "Drug interrupted" should be reported on the SAE form.*

OUTCOME

- Fatal – The study subject died.
- Not Recovered/Not Resolved – The AE was ongoing at the time of death or at the time the subject was lost to follow up.
- Recovered/Resolved – The AE resolved.
- Recovered/Resolved with Sequelae – The AE is considered resolved however there is residual sequelae. Some events do not return to baseline, such as metastasis or progression of disease; however, once these events are determined by the Investigator to be stable or chronic, the Investigator may consider the event to be resolved or resolved with sequelae.

- Recovering/Resolving – The AE is improving but is not yet completely recovered/resolved.
- Unknown – The outcome of the AE cannot be determined.

15.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

	Very good	Good	Fair	Poor	Very poor
Please check one box to show how you describe your current health:	☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Jenner Wing,
Cranmer Terrace,
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:

- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:

- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

Please check (✓) *one*:

My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

For each statement, please check (✓) ***the box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

For each statement, please check (✓) ***the box*** that applies to you ***these days:***

	True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . .

. . . .

. . . .

. . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Summary of Changes

Protocol - RIN-PH-201

Amendment 1 - 20November2015

Amendment 2 - 13September2016

Amendment 3 (Final Protocol) - 15February2017

Original Protocol (21 October 2015)

Amendment 1 (20 November 2015):

- Correction for diffusing capacity method to calculate DLCO
- Clarified the language in exclusion criteria 1
- Minor clarifying administrative text added throughout.

Amendment 2 (13 September 2016):

- Addition of exploratory optional evaluation of whole genome sequencing
- Time period for meeting inclusion (3 and 4) and exclusion criteria (8, 9 and 15) relative to baseline updated
- Change in definition for exacerbation of underlying lung disease
- Increased number of planned study sites
- Changed to screening urine pregnancy test
- Revised method to calculate DLCO for eligibility
- Revised to exclude background PAH therapies
- Clarifying administrative text added throughout.

Amendment 3 (15 February 2017):

- Eligibility criteria were updated to streamline and broaden entry to address slow study enrollment.
- Removed upper age limit
- Revised eligibility to broad ILD requirement for pulmonary hypertension
- Revised right heart catheterization criteria
- Remove DLCO eligibility criteria
- Revised criteria for time period for stable doses of nintedinab and pirefenidone relative to baseline
- Included subjects with Group 3 connective tissue disease with FVC < 70% requirement
- Modified Exclusion criteria 4, 5, 9, 10, 13 and 14 to broaden patient population in alignment with clinical practice
- Added exclusion for acute pulmonary embolism within 90 days of randomization
- Clarifying administrative text added throughout.

Original Statistical Analysis Plan - RIN-PH-201

27February 2019

Document Type:	Statistical Analysis Plan	**Protocol / Study No.:**	RIN-PH-201
First Draft Date:	10 APR 2018	**Total Number of Pages including Appendices:**	39
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Title:

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease

Author: [redacted]

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ABBREVIATIONS AND DEFINITIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BOCF	Baseline Observation Carried Forward
CHP	Chronic Hypersensitivity Pneumonitis
CPFE	Combined Pulmonary Fibrosis and Emphysema
CSR	Clinical study report
CT	Computed Tomography
CTD	Connective tissue disease
DLCO	Lung diffusion capacity
DMC	Data Monitoring Committee
DSP	Distance saturation product
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early termination
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HR	Heart rate
ICF	Informed consent form
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
ITT	Intent-to-treat
LOCF	Last observation carried forward
LRCF	Last rank carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurement
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAPm	Pulmonary artery pressure mean
PCWP	Pulmonary capillary wedge pressure
PFT	Pulmonary function test
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease

P-R	Time between P wave and beginning of QRS complex in electrocardiography
PT	Preferred Term
PVR	Pulmonary vascular resistance
Q-T	Electrocardiographic interval from beginning of QRS complex to end of the T wave
QTc	QT interval corrected for heart rate
QRS	Electrocardiographic wave interval
RHC	Right heart catheterization
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SpO_2	Saturation of Peripheral Capillary Oxygenation
TLC	Total lung capacity
WHO-DD	World Health Organization Drug Dictionary
WU	Wood Units

1 PREFACE

This plan provides further details of the planned analyses for the RIN-PH-201 study as presented in the study protocol. This plan, based on the original RIN-PH-201 study protocol dated 21 Oct 2015 and the subsequent study protocol amendments (latest version study protocol amendment 3 dated 15 February 2017), provides further details of the planned analyses stated in the study protocol as well as any additional planned analyses. Additional post hoc or unplanned analyses that are not defined in this statistical analysis plan (SAP) may be performed. Such analyses will be documented in the clinical study report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the safety and efficacy of inhaled treprostinil in subjects with Pulmonary Hypertension (PH) associated with Interstitial Lung Disease (ILD), including Combined Pulmonary Fibrosis and Emphysema (CPFE).

2.1 PRIMARY ENDPOINT

The primary endpoint is the change in 6-Minute Walk Distance (6MWD) measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

The secondary endpoints are:

1. Change in peak 6MWD from Baseline to Week 12
2. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
3. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints are:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD from Baseline to Week 8
3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:

  a. Hospitalization due to a cardiopulmonary indication
  b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart
  c. Death (all causes)
  d. Lung transplantation
5. Change in distance saturation product (DSP) from Baseline to Week 16

Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They will be specified in separate documents and not covered in this statistical analysis plan.

2.4 SAFETY ENDPOINTS

Safety endpoints will be used to evaluate safety based on the following assessments:

1. Adverse events (AEs)
2. Oxygenation:
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO2])
   b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
   a. Forced expiratory volume in 1 second (FEV1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalization due to a cardiopulmonary indication.
8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

3 STUDY DESIGN

This is a multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study. Subject eligibility will be based on the inclusion and exclusion criteria described in Section 4 of the protocol. Approximately 314 eligible subjects will be randomized to study

treatments (inhaled treprostinil or placebo) in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤350 meters versus >350 meters).

Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (randomization and first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo Screening assessments. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline pulmonary function tests (PFTs) and 6-Minute Walk Test (6MWT) used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Baseline Visit: The Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments, be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6MWT used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Treatment Phase: The Treatment phase consists of 5 study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit; at least 24 hours after the Week 15 Visit [final study visit/early termination {ET}]). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

4 SEQUENCE OF PLANNED ANALYSES

Interim Safety Analyses

Interim safety analyses are intended to be performed according to the Data Monitoring Committee (DMC) Charter. In particular, interim safety analyses are planned following the enrollment of approximately 25%, 50%, and 75% of subjects in the study, or at least annually (whichever is sooner). All analyses will be prepared by an independent external consultant and reviewed only by the independent DMC as defined in the DMC Charter. The Sponsor will only have access to the blinded study data during this process. Interim efficacy analyses are not planned in this study.

Dry-run Analysis Prior to Database Lock (Soft Lock)

At the completion of the study enrollment and prior to the database lock, a dry-run analysis is planned. This dry-run analysis utilizes a dummy randomization schedule in a blinded fashion. The purpose of the dry-run analysis is to verify programming of the analysis data sets and the planned tables, listings, and figures, and to identify any data issues. Programming and data issues identified through the dry-run process will be resolved prior to the database lock and study unblinding.

Final Analysis after Database Lock and Study Unblinding

After the database has been quality assured and locked, the treatment assignments will be provided to the sponsor's project statistician by the central randomization service and all planned analyses described in this document will be performed. By intent, no changes will be made to the clinical database after unblinding. However, any changes that are deemed necessary, after unblinding, will be clearly documented in the CSR.

5 SAMPLE SIZE CONSIDERATIONS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD, assuming a standard deviation of 75 meters.

The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

6 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population is defined as all subjects randomized into the study who received at least 1 dose of study drug. All ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses will be performed on this ITT population, unless otherwise specified.

The Safety population is defined as all subjects enrolled into the study who received at least 1 dose of study drug. All Safety population subjects will be counted in the group corresponding to the study drug received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

The Per-protocol population will include all subjects in ITT population, excluding subjects with major protocol deviations that may have an impact on the primary efficacy analyses. The major protocol deviations and the subject's exclusion from the Per-protocol population will be reviewed at a blinded data review meeting and documented prior to the database lock and the study unblinding.

7 INTERIM ANALYSES

There is no interim efficacy analysis for this study.

A DMC will be established for the study including physicians knowledgeable in the treatment of PH and a statistician. Throughout the course of the study the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DMC Charter. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC Charter. The Sponsor will only have access to blinded study data during this process. The details regarding the interim safety analysis will be included in a separate statistical analysis plan.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All the data collected in the electronic Case Report Form (eCRF) will be listed. In general, listings will be sorted by treatment group, subject number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), study day, and all relevant data collected in the eCRFs. For data collected on a fixed schedule, the assessment identifier or the nominal time point will also be included on the listing. Repeat or redundant observations within an assessment window and observations that do not fall within any predefined assessment window (and will, therefore, be excluded from summaries) will be flagged in these listings. Subjects who are not to be included in the analysis population (eg, Safety population, Per-protocol population) will be flagged.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group. For continuous variables, summary statistics will include the mean, standard deviation, median, minimum, and maximum. For summaries of non-normal data such as 6MWD, interquartile range (lower quartile, upper quartile) may also be included. Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal place than was collected. For discrete variables, summaries will include the frequency and percentage in each category. Percentages will be rounded to 1 decimal place. For all inferential analyses and descriptive comparisons, p-values will be rounded to 4 decimal places. Values less than 0.0001 will be denoted as <0.0001, and values greater than 0.9999 will be denoted as >0.9999 whenever practical, categories of discrete variables will be ordered and labelled as they appear in the eCRF, and all categories represented on the case report form will be included in summaries, even when they do not apply to any subjects in the study.

Unless otherwise specified, all statistical tests will be 2-sided at alpha level 0.05. All statistical calculations will be completed using SAS® Version 9.4 or above.

8.1 COVARIATES

The primary efficacy analyses of change in 6MWD at Week 16 will be adjusted for Baseline 6MWD (as a continuous variable). For sensitivity analyses of the primary efficacy endpoints and the secondary/exploratory endpoints with continuous variables, the baseline measure will always be the covariate.

8.2 EXAMINATION OF SUBGROUPS

For primary efficacy endpoints of change in 6MWD at Week 16, subgroup analyses will be performed. These subgroups will include:

- Etiology of ILD (Idiopathic Interstitial Pneumonia [IIP], Chronic Hypersensitivity Pneumonitis [CHP], Occupational, CPFE, Connective Tissue Disease [CTD], and Other)
- Baseline walk categories (≤350 meters versus >350 meters, ≤ median baseline 6MWD versus > median baseline 6MWD)
- ILD disease severity as measured by Baseline DLCO (<40% predicted versus ≥40% predicted)

- Sex (male versus female)
- Pulmonary Vascular Resistance (PVR) (<4 versus ≥4 Wood Units [WU])
- Age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths)

No Type 1 error adjustments will be performed for these subgroup analyses.

8.3 PREMATURE DISCONTINUATION AND MISSING DATA

8.3.1 Missing Data Handling for 6MWD

For the analysis of 6MWD, subjects may not have completed the treatment with study drug prior to the Week 16 visit for the following reasons: death, progressive disease, AE, withdrawal of consent by the subject, protocol violation, loss to follow-up, termination of study by the sponsor, or withdrawal for other reasons. Every attempt must be made to perform all efficacy assessments immediately prior to premature termination of study drug or withdrawal from the study. In addition, subjects still receiving study drug may be too critically ill to perform the 6MWT, resulting in missing data for that assessment.

Every effort should be made to complete all scheduled study assessments for all randomized subjects. Although attempts will be made to continue to collect data after termination of study drug, these data are being collected for sensitivity analyses and descriptive purposes only. Assessments performed after treatment unblinding or more than 24 hours after the last dose of study drug will not be included in the main analyses of peak 6MWD.

For subjects whose peak 6MWD measures at Week 4, Week 8, Week 12, or Week 16 are missing, the missing value will be imputed as described in Table 8-1.

Table 8-1 Imputation Rules for Peak 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening event	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Last (peak) Observation Carried Forward (LOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test.

For subjects whose trough 6MWD measures at Week 15 are missing, the missing values will be imputed as described in Table 8-2.

Table 8-2 Imputation Rules for Trough 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Baseline Observation Carried Forward (BOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test, BOCF, Baseline observation carried forward.

8.3.2 Missing Data Handling for Other Efficacy Assessments

For the secondary endpoints of NT-proBNP, the missing value at Week 16 will be imputed using LOCF. If the NT-proBNP measure at Baseline is missing, the change from Baseline will not be calculated. The subject will not be included in the analyses.

For exploratory endpoints of SGRQ, biomarkers, and DSP, the missing values will not be imputed, and all analyses will be based on the observed cases.

8.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The primary efficacy endpoint of change in 6MWD measured at peak exposure from Baseline to Week 16 will be tested at alpha level 0.05. If the primary efficacy endpoint is statistically significant at alpha level 0.05, the statistical tests for secondary efficacy endpoints will be performed.

To control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed-sequence) testing procedure. The change from Baseline in peak 6MWD at Week 12 will be tested at a 2-sided Type 1 error rate of 0.05. The subsequent tests for change from Baseline in NT-proBNP at Week 16, and then the change from Baseline in trough 6MWD at Week 15, will be tested sequentially only if the preceding test is statistically significant.

8.5 DERIVED AND TRANSFORMED DATA

Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:

- Hospitalization due to a cardiopulmonary indication
- Decrease in 6MWD >15% from Baseline directly related to disease under study at 2 consecutive visits and at least 24 hours apart
- Death (all causes)
- Lung transplantation

Time to clinical worsening is calculated as described in Table 8-3.

Table 8-3 Derivation of Time to Clinical Worsening

Parameter	Scenario	Formula	Status
Time to clinical worsening (weeks)	Subjects with clinical worsening event reported	= (Worsening date – Randomization date +1)/7	0 (event)
	Subjects who died during the study	= (Death date – Randomization date +1)/7	0 (event)
	Subjects without clinical worsening event during the study	= (Last assessment date – Randomization date +1)/7	1 (censored)
	Subjects discontinued from the study prematurely	= (Last assessment date – Randomization date +1)/7	1 (censored)

For subjects with clinical worsening due to decrease from Baseline in 6MWD, a confirmatory 6MWT should be conducted. The event time is based on the date of the confirmatory 6MWT. If the confirmatory 6MWT is not conducted, the event time is then based on the date of the first 6MWT.

Distance Saturation Product (DSP) is calculated as follows:

Parameter	Formula
DSP (m%)	= (Distance walked in meters) x (Lowest oxygen saturation recorded during the 6MWT)

Abbreviations: 6MWT, 6-Minute Walk Test; DSP, Distance Saturation Product.

Adjustments to the QT intervals will be calculated as follows:

Parameter	Formula
QTc (Bazett)	$= \text{Q-T}/\sqrt{60/\text{HR}}$
QTc (Fridericia)	$= \text{Q-T}/\sqrt[3]{60/\text{HR}}$

Abbreviations: HR, Heart rate; QTc, Q-T interval corrected for heart rate; Q-T, Electrocardiographic interval from beginning of QRS complex to end of the T wave.

8.6 ASSESSMENT WINDOWS

For any data summarized by scheduled visit, an analysis visit window will be used. The scheduled visits, as recorded on the eCRFs, and the corresponding target days and study day intervals are specified in Table 8-4. The analysis visit window will be derived based on the information specified in Table 8-4.

In the protocol, the visit window for Week 4, Week 8, Week 12, and Week 16 is ±5 days and the visit window for the Week 15 visit is ±5 days and at least 24 hours prior to Week 16 6MWT. In order to allow slotting of discontinuation visits and visits outside the planned schedule, the visit windows have been expanded for analysis purposes for Week 4, Week 8, Week 12, and Week 16. The nominal study visit identified as Week 15 in the eCRF will be used for the Week 15 visit provided it is at least 24 hours prior to Week 16 6MWT or there is no Week 16 visit.

Table 8-4 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
ECGs, SGRQ:		
Baseline	1	Study Day ≤1 (prior to the date of the first dose)
Week 16	113	1 < Study Day
PFTs, Clinical laboratory assessments and NT-proBNP:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 8	57	1 < Study Day ≤ 71
Week 16	113	99 < Study Day
Peak 6MWT:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 16	113	99 < Study Day
Trough 6MWT:		
Week 15	106	Nominal study visit and at least 24 hours prior to Week 16 6MWT or no Week 16 visit
Vital signs, Pulse oximetry:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 15	106	Nominal study visit and at least 24 hours prior to Week 16 6MWT or no Week 16 visit
Week 16	113	99 < Study Day

Note: Study Day = (Assessment Date) − (First Dosing Date) +1
Abbreviations: 6MWT, 6-Minute Walk Test; ECG, Electrocardiogram; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PFT, Pulmonary function test.

Multiple Evaluations within the Same Analysis Window

After all the observations have been slotted based on the table above, if there are multiple valid observations for an assessment within an assigned analysis visit window, only 1 of these observations will be used for summary statistics and analyses. The observation to be used is determined using the following hierarchy (in decreasing order):

- The observation closest to the target study day
- The later observation if 2 observations are equally close to the target study day

For missing values where the LOCF algorithm is applied, it is always the last valid observation on treatment carried forward, even though this might not be the observation obtained by the above hierarchy and used in the summaries by visit window.

9 STUDY POPULATION

Unless otherwise specified, all efficacy analyses will be performed on the ITT population and all safety analyses will be based on the Safety population. In the ITT population, the treatment assignment is based on the assignment upon randomization. In the Safety population, the treatment assignment is based on the actual treatment the subject received.

The comparability between the 2 treatment groups will be checked for demographic and baseline characteristics. The p-values from Fisher's exact test (for discrete variables) or Group t-test or Wilcoxon rank sum test (for continuous variables) will be included on summaries but are not intended to be used to test formal hypotheses. For these comparisons, missing or unknown values will be excluded from the calculations.

9.1 SUBJECT ACCOUNTABILITY

All subjects' disposition information will be listed by individual subject number, including the analysis population the subjects belong to, premature study drug discontinuation status, primary reason for premature study drug discontinuation, premature study discontinuation status, primary reason for premature study discontinuation, number of days on the study drug, and enrollment in the open label extension study (RIN-PH-202).

The listing of subject accountability will include the dates of informed consent and randomization, the first study drug dose, last study drug dose, and last assessment dates and times, and the last dose and assessment weeks. Whether subjects received the study drug, whether subjects completed the Weeks 4, 8, 12, 15, 16 assessments, and study discontinuation status will be summarized.

Information regarding whether each subject is included in each analysis population (see Section 6) will be listed. If a subject is not included in a particular analysis population, the reason for exclusion will be noted on the listing. Also noted on the listing will be the randomized treatment assignment and the actual treatment subjects have received. The summary will include the frequency and percentage of all subjects in each analysis population.

The stratification information used in the random assignment of subjects to treatment group (from the central randomization database) will be listed, including date and time of randomization and Baseline 6MWD category (≤350 meters versus >350 meters). Status of the treatment blind, and if broken, date/time of blind broken will be listed. The number of subjects in each stratum will be summarized by treatment group and overall.

9.2 PROTOCOL DEVIATIONS

The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment, whether all eligibility criteria were met (Yes/No), and a list of any specific entry criteria not met. This listing will also include the protocol version that the subject was enrolled under. Entry criteria violations will be summarized by treatment group and overall.

Additional protocol deviations will be documented throughout the study. All deviations will be reviewed by the clinical team prior to database lock and those that might affect subject safety or efficacy outcomes will be considered ‘Major’. All other deviations will be classified as ‘Minor’. Protocol deviations will be listed, including the date of the deviation, the type of deviation, the severity of the deviation (Major/Minor), and a description of the deviation. The protocol deviations will also be summarized by treatment group and overall.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

All demographic data will be listed for all subjects, including assessment date, date of birth, country, age, sex, ethnicity, race, weight, height, and body mass index (BMI). Age, age category (<65 years of age, 65 to <80 years of age, and ≥80 years of age), sex, ethnicity, race,

height, weight, and BMI will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher's exact test (for age category, sex, ethnicity, and race) and group t-test or Wilcoxon rank sum test (for age, weight, height, and BMI) comparing treatment groups.

9.3.2 Baseline Characteristics

Baseline characteristics will include the Baseline 6MWD, Baseline NT-proBNP, and hemodynamic parameters. Hemodynamic parameters, measured by the right heart catheterization (RHC), will include PVR, pulmonary artery pressure mean (PAPm), pulmonary capillary wedge pressure (PCWP), and details concerning vasodilator testing will be listed and summarized.

9.3.3 Medical History and PH-ILD History

All significant past or ongoing medical conditions will be listed for all subjects. The listing will include the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for each condition listed, and whether the condition is ongoing at Randomization. These medical conditions will be summarized by PT within each SOC.

Information related to subjects' PH-ILD history will be listed. The listing will include the date of initial PH diagnosis, years since PH diagnosis, etiology of ILD (including IIP subcategory), date of confirmatory computed tomography (CT) scan, whether ILD diagnosis confirmed with a lung biopsy, and if so, the date of lung biopsy.

The current ILD diagnosis (ILD category) and IIP subcategory, time since PH diagnosis, and whether ILD diagnosis was confirmed via lung biopsy will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher's exact test (for current ILD diagnosis) or Wilcoxon rank sum test (for time since diagnosis) comparing treatment groups.

9.3.4 Concomitant Medications

All concomitant medications specified on the eCRF will be mapped to a standard name using the World Health Organization Drug Dictionary (WHO-DD).

The standard name and verbatim term of all concomitant medications will be listed for all subjects. This listing will include the date started (or indication that drug was ongoing at randomization), date discontinued (or indication that drug was ongoing at end of study), and the condition(s) treated/indication(s). If a subject received no medications, this will be indicated on the listing. Summary of concomitant medications present at Baseline and summary of concomitant medications added during the study will include the frequency and percentage of subjects in each treatment group receiving each drug (by coded standard name).

10 EFFICACY ANALYSES

Except where otherwise noted, all efficacy analyses will only be performed on the ITT population (see Section 6).

10.1 PRIMARY EFFICACY MEASURES

10.1.1 Primary Efficacy Analyses

10.1.1.1 Hypothesis

The primary efficacy endpoint of peak 6MWD assesses if inhaled treprostinil will increase the distance traversed in the peak 6MWT at Week 16 over placebo in subjects with PH-ILD. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2,$$

where μ_1 and μ_2 are the median change from Baseline in 6MWD of the inhaled treprostinil and placebo treatment groups, respectively.

10.1.1.2 Primary Efficacy Analysis

All 6MWT data will be listed for all subjects. For each scheduled assessment, this listing will include the date test was performed (or date test was intended to be performed if subject is unable to attempt the test), start time of the test, nominal time point, last treatment dose, hours from last treatment dose to 6MWT start, if walk was attempted, total distance walked (in meters), whether subject received oxygen during the test, amount of supplemental oxygen, and any circumstances that adversely affected the walk (if any) including reason for not

attempting test (if any). The trough 6MWT measure will also be indicated. In addition, a listing of 6MWD with imputed values will be included for both peak and trough 6MWD data.

For the primary efficacy analysis, the effect of inhaled treprostinil versus placebo on change in peak 6MWD at Week 16 will be evaluated via analysis of covariance (ANCOVA). Change from Baseline in peak 6MWD is the dependent variable, and treatment and Baseline 6MWD are covariates in this ANCOVA model. Least squares means and standard errors for each treatment group, the least squares mean difference and its standard error, as well as a 95% confidence interval for the treatment group difference and p-value for treatment group comparison will be calculated from the ANCOVA model. This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. The LOCF algorithm will be applied.
4. ANCOVA will be conducted based on the pseudo SAS code:

```
proc glm;
  class Treatment;
  model DistC = Treatment Dist0;
run;
```

where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.

If the ANCOVA assumptions are violated, the primary efficacy analysis will be based on non-parametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (Koch 1990, Koch 1998, Stokes 2000). Specifically, a Cochran-Mantel-Haenszel mean score test will be used on the standardized mid-ranks (ie, overall rank divided by the number of ranks +1, or “modified ridit” scores) of the residuals from an ordinary least squares regression with change from Baseline in peak 6MWD at Week 16 as a linear function of distance walked at Baseline (as a continuous variable). This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. Calculate ranks. The pseudo SAS code is as follows:

```
proc rank nplus1 ties=mean out=ranks;
  var DistC Dist0;
run;
```

   where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.
4. Linear regression model will be fit using the rank values generated above. The pseudo SAS code is as follows:

```
proc reg data=ranks noprint;
  model DistC=Dist0;
  output out=residual r=resid;
run;
```

   where DistC is the rank value of the change from Baseline in peak 6MWD at Week 16 and Dist0 is the rank value of the baseline measure of the 6MWD.
5. A mean score test, using the values of the residuals as scores, compares the treatment groups. Cochran-Mantel-Haenszel mean score statistic and p-value will be calculated, using the NOPRINT and CMH2 options in the TABLES statement of the FREQ procedure of SAS. The pseudo SAS code is as follows:

```
proc freq data=residual;
  tables Treatment*Resid / noprint cmh2;
run;
```

   where Treatment indicates the randomized treatment group, and Resid represents the residuals obtained from the above linear regression models.

In addition to the p-value from the non-parametric method described above, the Wilcoxon rank sum test and the Hodges-Lehmann estimate of median difference (as an estimate of location shift between 2 treatment groups for the placebo-controlled treatment effect) will be provided. The Wilcoxon rank sum test and the Hodges-Lehmann estimate can be obtained through the following pseudo SAS code:

```
proc npar1way hl Wilcoxon;
   class treatment;
   var DistC;
run;
```

where DistC is the change from Baseline in peak 6MWD at Week 16.

10.1.1.3 Sensitivity and Subgroup Analyses

In order to analyze walk distances at each scheduled assessment, values for missing or excluded assessments up to and including Week 16 will be imputed according to rules described in Section 8.3.1.

To further support the robustness and assess the sensitivity of the primary efficacy analysis of change in peak 6MWD at Week 16 (provided that the primary analysis yields significant results), the above non-parametric and parametric analyses and summaries will be repeated using each of the following modifications (as data permit):

- The Per-protocol population will be used instead of the ITT population
- Missing data imputation using the LOCF method (based on peak values)
- Missing data imputation using the last rank carried forward (LRCF) method (based on peak values) (O'Brien 2005)
- Using only the observed values without imputation
- Including data collected after termination of the study drug
- ITT population excluding subjects with a reported exacerbation within 3 days of the Week 16 peak 6MWT measure
- Stratified by ILD etiology categories (IIP, CHP, Occupational, CPFE, and Other)
- Stratified by Baseline 6MWD categories (≤350 meters versus >350 meters, ≤median baseline 6MWD versus > median baseline 6MWD)
- Stratified by Baseline DLCO percent predicted (<40% versus ≥40%)
- Stratified by Baseline pulmonary vascular resistance (PVR) (<4 versus ≥4 WU)
- Stratified by sex (male versus female)
- Stratified by age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Stratified by study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths).

A longitudinal data analysis using mixed model repeated measurement (MMRM) will also be performed to estimate the treatment difference in change in peak 6MWD at Week 16. The MMRM will include the change from Baseline in peak 6MWD as the dependent variable, treatment, week, and treatment by week interaction as fixed effects, and Baseline 6MWD as a covariate. An unstructured variance/covariance structure shared across treatment groups will be used to model the within-subject errors.

An additional sensitivity analysis will be performed for percent change from Baseline to Week 16 in peak 6MWD using the same approach as the primary analysis method where the percent change from Baseline is calculated as

$$\frac{\text{peak 6MWD at Week 16} - \text{Baseline 6MWD}}{\text{Baseline 6MWD}} \text{X } (100\%).$$

In addition, the impact of Baseline hemodynamics and Baseline PFTs, including PVR, PAPm, PCWP, FEV_1, FVC, TLC, and DLCO as continuous variables, on peak 6MWD, will be explored using the regression approach.

10.2 SECONDARY EFFICACY MEASURES

Secondary efficacy endpoints include the following:

- Change in peak 6MWD from Baseline to Week 12
- Change in plasma concentration of NT-proBNP from Baseline to Week 16
- Change in trough 6MWD from Baseline to Week 15

As specified in Section 8.4 above, the hierarchical (fixed-sequence) testing procedure will be employed to control the overall alpha level at 0.05.

10.2.1 Change in Peak 6MWD at Week 12

The methodology for primary efficacy analysis of change in peak 6MWD at Week 16 will also be carried out for the Week 12 assessment, as described above in Section 10.1.1.2.

10.2.2 Change in NT-proBNP at Week 16

The efficacy endpoint of change in NT-proBNP assesses if inhaled treprostinil decreases the level of NT-proBNP at Week 16 over placebo in subjects with PH-ILD. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2,$$

where μ_1 and μ_2 are the median change from Baseline to Week 16 in NT-proBNP of the inhaled treprostinil and placebo treatment groups, respectively.

The NT-proBNP values will be listed for all subjects, including the nominal time point, collection date/time, normal range and "High/Low" flag. The values and their respective changes from Baseline will be summarized for each assessment. The difference between treatment groups for the change from Baseline to Week 16 will be tested using the analysis of covariance with change from Baseline in NT-proBNP as the dependent variable, treatment as the fixed effect, and Baseline NT-proBNP as the covariate. The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model BNP_C=Treatment BNP_B;
run;
```

where BNP_C is the change from Baseline to Week 16 in NT-proBNP and BNP_B is the NT-proBNP at Baseline.

If assumptions (normality and equal variance) for the parametric test are violated, the nonparametric Wilcoxon rank-sum test will be used. For subjects who do not have NT-proBNP measurements at Week 16, the LOCF imputation will be used. The analyses will also be performed for the data without imputation for the missing measures.

As an exploratory analysis, the NT-proBNP at Week 8 will be analysed using the same method as the NT-proBNP at Week 16.

10.2.3 Change in Trough 6MWD at Week 15

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the change in trough 6MWD from Baseline to Week 15. Missing trough 6MWD will be imputed as described in Table 8-2 in Section 8.3.1. The analysis will be repeated to include only subjects with trough 6MWD at Week 15 (ie, missing trough 6MWD at Week 15 is not imputed).

10.3 EXPLORATORY EFFICACY MEASURES

Exploratory efficacy endpoints include the following parameters:

- Change in peak 6MWD from Baseline to Week 4
- Change in peak 6MWD from Baseline to Week 8
- Change in quality of life as measured by SGRQ from Baseline to Week 16
- Time to clinical worsening will be evaluated as an exploratory endpoint from the time to randomization until 1 of the following criteria are met:
  a. Hospitalization due to a cardiopulmonary indication
  b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  c. Death (all causes)
  d. Lung transplantation
- Change in DSP from Baseline to Week 16

10.3.1 Change in Peak 6MWD at Weeks 4 and 8

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the assessments obtained at Week 4 and Week 8.

10.3.2 Change in SGRQ at Week 16

The responses to the SGRQ questionnaire at Baseline and Week 16 will be converted to the Total score and 3 domain scores according to the SGRQ manual (Jones 2002). Scores for Total and each domain will range from 0 to 100, with higher scores indicating more limitations. Both individual item responses as well as calculated scores will be listed. The change from Baseline for the Total and 3 domain scores (Symptoms, Activity, and Impacts) will be calculated.

The Total score and for the 3 domain scores as well as their changes from Baseline will be summarized by treatment group using descriptive statistics.

For the Total score and each of the 3 domain scores, treatment differences (inhaled treprostinil vs. placebo) will be tested by using analysis of covariance with change from Baseline as the dependent variable, treatment as a fixed effect, and baseline score as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model Score_C=Treatment Score_B;
run;
```

where Score_C is the change from Baseline in Total score or each of the 3 domain scores and Score_B is the corresponding score at Baseline.

10.3.3 Time to Clinical Worsening

- Data on the clinical worsening assessment page of the eCRF will be used to determine clinical worsening status. Investigator-reported clinical worsening events including the date (study day) of the event, category of the clinical worsening event, Baseline 6MWD, first 6MWT details, and second 6MWT details will be listed. The time to clinical worsening will be calculated according to the rules described in Table 8-3 in Section 8.5.

The number and percentage of subjects with any clinical worsening and with each category of clinical worsening will be summarized by treatment group. Time to clinical worsening will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. A tabular summary of this analysis will include the number of subjects at risk (sample size), estimated median duration, and a 95% confidence interval for the median duration for each treatment group. The log-rank test, adjusted for Baseline 6MWD category, will be used to calculate the p-value for treatment differences in the ITT population.

The SAS Procedure LIFETEST will be used. The pseudo SAS statements are listed below:

```
proc lifetest;
  time TimeToWorsening*Censor_Status(1);
  strata B_6MWD / group = Treatment test=all;
run;
```

where B_6MWD denotes the categorical Baseline 6MWD variable (≤350 meters versus >350 meters).

In addition, the Cox proportional hazards model will be fit to obtain the hazard ratio and its associated 95% confidence interval. The model will include treatment and Baseline 6MWD as explanatory variables. The SAS procedure PHREG will be used. The pseudo SAS statements are listed below:

```
proc phreg;
  class Treatment;
  model TimeToWorsening*Censor_Status(1) = Treatment Dist0
        / risklimits alpha=0.05 ties=efron;
  assess var=Dist0 ph;
run;
```

where Dist0 denotes the Baseline 6MWD variable (continuous). If it is determined that the proportional hazards assumption does not hold for Baseline 6MWD, a stratified analysis will be conducted. The above SAS code will be amended to remove Dist0 from the model statement and add the ‘strata B_6MWD;’ statement.

If the proportional hazards assumption does not hold for the Cox model, the restricted mean survival time (RMST) and its associated standard error will be calculated for each treatment group at Week 16 (Royston 2013). A 95% confidence interval will be constructed for the difference in RMST between the 2 treatment groups at Week 16.

10.3.4 Change in DSP

The DSP will be calculated, and DSP results will be included in the data listing for pulse oximetry. DSP values and their respective changes from Baseline to Week 16 will be summarized by treatment group. The difference between treatment groups for the change from Baseline to Week 16 will be tested using analysis of covariance with change from Baseline in DSP as the dependent variable, treatment as a fixed effect, and Baseline DSP measure as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model DSP_C=Treatment DSP_B;
run;
```

where DSP_C is the change from Baseline to Week 16 in DSP (m%) and DSP_B is DSP at Baseline.

In addition, the DSP at Week 4, Week 8, and Week 12 will each be analyzed in the same way as the DSP at Week 16.

11 HEALTH OUTCOMES

11.1 QUALITY OF LIFE MEASURES

Quality of life was assessed using SGRQ. The analyses of SGRQ are described in Section 10.3.2.

11.2 RESOURCE UTILIZATION MEASURES

Hospitalizations and hospitalizations related to cardiopulmonary indications are collected during the study. The analysis is discussed in Section 12.6.2.

12 SAFETY ANALYSES

All safety analyses will be performed only on the Safety population (see Section 6).

12.1 EXTENT OF EXPOSURE

All study drug dosing will be listed for all subjects. The listing will include initial dose (number of breaths for each session and number of breaths for the day) and date of this initial dose and dose and date of each subsequent dose change. Dosing at Weeks 4, 8, 12, 15, and 16 will be summarized for subjects still receiving study drug at each of these assessments. The summary will include both the numeric summaries and the categorical summaries for number of breaths per session as well as the number of breaths per day. If study drug is dosed differently across different sessions on the same day, the maximum number of breaths is used for summarization. Summary of overall duration of exposure will be included as well as the

final dose (breath/session) and the maximum study drug dose (breath/session) reached for each subject (numerically and categorically).

For study treatment compliance, the number and percentage of days with dose >0 breaths will be calculated and summarized.

12.2 ADVERSE EVENTS

All AEs will be coded to the appropriate PT and SOC using MedDRA. AEs will be listed by treatment group including all details recorded on the eCRF plus an indicator of whether the event was treatment-emergent. The AE listings will include the AE verbatim term and its corresponding PT and SOC.

The AE summaries will be limited to include only treatment-emergent AEs. Treatment-emergent AEs are those AEs with onset date equal to or after the start date of the study drug. The non-treatment-emergent AEs (the AEs occur after signing the informed consent form but before receiving study drug) will be listed but not included in summary tables.

All summaries will include the number and percentage of subjects experiencing each type of adverse event and the total number of each type of adverse event, in order of overall frequency and/or SOC. Serious adverse events (SAE) and non-serious AEs will also be summarized by SOC and PT.

The total number of AEs and the AE rates will be calculated and summarized for each display, as appropriate. The AE rate will be calculated as the total number of AEs divided by the total patient years of exposure to study drug per treatment group.

Adverse events possibly or probably related to study drug will be summarized. An AE summary by severity (mild, moderate, and severe) will also be provided.

Separate listings and summary tables will be provided for all SAEs, AEs leading to the discontinuation of study drug, and all deaths during the study (if data permit). For listing of deaths, information for all subjects who die during the study period from the randomization to the end of study (including 30 days after the last study treatment dosing) will be included.

12.3 OXYGENATION

Oxygenation is measured by pulse oximetry (SpO_2 and supplemental oxygen requirement [L/min]) during each 6MWT. At each 6MWT, pulse oximetry (for SpO_2) will be measured at pre-walk, during walk, and post-walk. During walk, the lowest SpO_2 will be recorded. All pulse oximetry results along with the collection date/time (study day) will be listed. Heart rate will be listed for pre-walk and post-walk only.

The SpO_2 will be summarized by treatment group, visit, and time point (pre-walk, during walk, and post-walk). The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from Baseline calculations, the measurements pre-walk, during walk, and post walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk, during walk, and post-walk at Baseline.

In addition, for each time point at each visit, the number and percentage of subjects with SpO_2 or lowest SpO_2 <80%, ≥80 to <88, and ≥88%, and with SpO_2 dropping ≥10% during walk and/or post-walk from pre-walk will be summarized by treatment group.

At each visit, supplemental oxygen requirements will be collected at rest and during 6MWT. These data will be listed, including visit, 6MWT date/time, and oxygen use at rest and during walk. The number and percentage of subjects requiring supplemental oxygen use at rest and during the 6MWT will also be summarized by the treatment group. Supplemental oxygen level at rest at each visit and the corresponding changes from Baseline will be summarized by treatment group.

Heart rate will be summarized by treatment group, by time point (pre-walk and post-walk) and visit. The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from baseline calculations, the measurements pre-walk and post-walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk and post-walk at Baseline.

12.4 PULMONARY FUNCTION TESTS

The PFT parameters include:

- Forced expiratory volume in 1 second (FEV_1)
- Forced vital capacity (FVC)
- Total lung capacity (TLC)
- Lung diffusion capacity (DLCO)

Only pre-bronchodilator values will be recorded on eCRF and will be listed. All PFT parameters and their change from baseline values will be summarized by treatment group and visit.

For FEV_1 results, the number and percentage of subjects with FEV_1 decreasing more than 20% from Baseline at any post-Baseline Visit will be summarized by treatment group.

12.5 CLINICAL LABORATORY EVALUATIONS

Blood samples will be taken at Screening and/or Baseline, Week 8, and Week 16. All samples will be sent to a central laboratory for evaluation of clinical chemistry and hematology.

12.5.1 Clinical Chemistry

The following clinical chemistry parameters will be evaluated by the central laboratory:

Parameter	Units
Sodium	mmol/L
Potassium	mmol/L
Bicarbonate	mmol/L
Chloride	mmol/L
Total bilirubin	umol/dL
Alkaline phosphatase	U/L
Alanine aminotrasferase	U/L
Aspartate aminotransferase	U/L
Urea nitrogen	mmol/dL
Creatinine	umol/L
Calcium	mmol/L
Albumin	g/L

Values that are "High" or "Low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L," respectively. All parameters will be listed for all subjects and assessments, along with their respective "High/Low" flags.

Values of these parameters at each visit, and their corresponding changes from Baseline will be descriptively summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who had "Low," "Normal," or "High" Baseline values, then subsequently had "Low," "Normal," or "High" follow-up values at each visit will be presented in a shift summary.

12.5.2 Hematology

The following hematology parameters will be evaluated by the central laboratory:

Parameter	Units
Hemoglobin	g/dL
Hematocrit	%
Red blood cell count	10^6/uL
Red blood cell morphology	
White blood cell count	10^3/uL
Platelet count	10^3/uL

Values that are "High" or "Low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L," respectively. All parameters will be listed for all subjects and assessments, along with their respective "High/Low" flags.

Numeric values of these parameters at each visit and their corresponding changes from Baseline will be summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who have "Low," "Normal," or "High" Baseline values, then subsequently have "Low," "Normal," or "High" follow-up values at each assessment will be presented in a shift summary.

12.5.3 Pregnancy Test

Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit. All pregnancy tests will be performed at study sites. Pregnancy status during the study will be listed.

12.6 OTHER SAFETY MEASURES

12.6.1 Electrocardiograms

All ECG assessments will be listed for all subjects. This listing will include the heart rate, the ECG interval from the beginning of QRS complex to end of the T wave (Q-T interval), the QT interval corrected for heart rate (QTc) (calculated using formulas by both Bazett and Fridericia as described in Section 8.4), the time between P wave and beginning of QRS complex in ECG (P-R interval), the electrocardiographic wave (QRS) duration, ECG results (Normal/Abnormal), whether there were clinically significant changes from Screening visit, whether abnormalities were present, and details and comments on any abnormalities. The ECG results at Baseline and changes at Week 16 will be descriptively summarized by treatment group. In addition, for QTc intervals calculated using both the Bazett and Fridericia methods, the number and percent of subjects with values ≥500 msec and the number and percent of subjects with changes from Screening of <30 msec, 30 to <60 msec, and ≥60 msec will be presented. Additionally, each abnormality will be summarized by number and percentage of subjects reporting at each visit by treatment group.

12.6.2 Hospitalizations

Details for all hospitalizations will be listed. Number of hospitalizations for cardiopulmonary indications and total duration of hospitalization for cardiopulmonary indications will be summarized for each treatment group as well as overall number of hospitalizations and total duration regardless of indication.

12.6.3 Vital Signs

All vital sign assessments will be listed for all subjects. This listing will include height, weight, body mass index (BMI), heart rate, systolic and diastolic blood pressures, respiratory

rate, and temperature. The vital sign results at each assessment and changes for each post-Baseline assessment will be descriptively summarized by treatment group.

12.6.4 Exacerbations of Underlying Lung Disease

Exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Number of subjects with exacerbation of underlying lung disease will be summarized for each treatment group and included in the overall AE summary table. A listing of these events will also be provided.

13 PHARMACOKINETICS

No pharmacokinetic measures will be assessed in this study.

14 REFERENCES

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Final Statistical Analysis Plan - RIN-PH-201

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Author: [redacted]

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ABBREVIATIONS AND DEFINITIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BOCF	Baseline Observation Carried Forward
CHP	Chronic Hypersensitivity Pneumonitis
CPFE	Combined Pulmonary Fibrosis and Emphysema
CSR	Clinical study report
CT	Computed Tomography
CTD	Connective tissue disease
DLCO	Lung diffusion capacity
DMC	Data Monitoring Committee
DSP	Distance saturation product
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early termination
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HR	Heart rate
ICF	Informed consent form
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
ITT	Intent-to-treat
LOCF	Last observation carried forward
LRCF	Last rank carried forward
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurement
NT-proBNP	N-Terminal pro-brain natriuretic peptide
PAPm	Pulmonary artery pressure mean
PCWP	Pulmonary capillary wedge pressure
PFT	Pulmonary function test
PH	Pulmonary hypertension

PH-ILD	Pulmonary hypertension associated with interstitial lung disease
P-R	Time between P wave and beginning of QRS complex in electrocardiography
PT	Preferred Term
PVR	Pulmonary vascular resistance
Q-T	Electrocardiographic interval from beginning of QRS complex to end of the T wave
QTc	QT interval corrected for heart rate
QRS	Electrocardiographic wave interval
RHC	Right heart catheterization
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SpO_2	Saturation of Peripheral Capillary Oxygenation
TLC	Total lung capacity
WHO	World Health Organization
WU	Wood Units

1 PREFACE

This plan provides further details of the planned analyses for the RIN-PH-201 study as presented in the study protocol. This plan, based on the original RIN-PH-201 study protocol dated 21 Oct 2015 and the subsequent study protocol amendments (latest version study protocol amendment 3 dated 15 February 2017), provides further details of the planned analyses stated in the study protocol as well as any additional planned analyses. Additional post hoc or unplanned analyses that are not defined in this statistical analysis plan (SAP) may be performed. Such analyses will be documented in the clinical study report (CSR).

1.1 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The ordering of secondary and exploratory endpoints were re-ordered in the SAP Amendment 1 and differ from the order specified in RIN-PH-201 Protocol Amendment 3. In the protocol, time to clinical worsening was identified as an exploratory endpoint. In the SAP Amendment 1 analyses, time to clinical worsening will be analyzed as a secondary endpoint.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the safety and efficacy of inhaled treprostinil in subjects with Pulmonary Hypertension (PH) associated with Interstitial Lung Disease (ILD), including Combined Pulmonary Fibrosis and Emphysema (CPFE).

2.1 PRIMARY ENDPOINT

The primary endpoint is the change in 6-Minute Walk Distance (6MWD) measured at peak exposure from Baseline to Week 16.

2.2 SECONDARY ENDPOINTS

The secondary endpoints are:

1. Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Week 16
2. Time to clinical worsening calculated as the time from randomization until 1 of the following criteria are met:
   a. Hospitalization due to a cardiopulmonary indication

   b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits, and at least 24 hours apart
   c. Death (all causes)
   d. Lung transplantation
3. Change in peak 6MWD from Baseline to Week 12
4. Change in trough 6MWD from Baseline to Week 15

2.3 EXPLORATORY ENDPOINTS

Exploratory endpoints are:

1. Change in peak 6MWD from Baseline to Week 4
2. Change in peak 6MWD from Baseline to Week 8
3. Change in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) from Baseline to Week 16
4. Change in distance saturation product (DSP) from Baseline to Week 16

Exploratory endpoints of optional evaluation are change in biomarkers from Baseline to Week 16, and optional evaluation of whole genome sequence. They will be specified in separate documents and are not covered in this SAP.

2.4 SAFETY ENDPOINTS

Safety endpoints will be used to evaluate safety based on the following assessments:

1. Adverse events (AEs)
2. Oxygenation:
   a. Pulse oximetry (saturation of peripheral capillary oxygenation [SpO2])
   b. Supplemental oxygen requirement (L/min)
3. Pulmonary function:
   a. Forced expiratory volume in 1 second (FEV1)
   b. Forced vital capacity (FVC)
   c. Total lung capacity (TLC)
   d. Lung diffusion capacity (DLCO)
4. Clinical laboratory parameters
5. Vital signs
6. Electrocardiograms (ECG)
7. Hospitalization due to a cardiopulmonary indication.

8. Exacerbations of underlying lung disease; defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

3 STUDY DESIGN

This is a multicenter, randomized, double-blinded, placebo-controlled, 16-week, parallel group study. Subject eligibility will be based on the inclusion and exclusion criteria described in Section 4 of the protocol. Approximately 314 eligible subjects will be randomized to study treatments (inhaled treprostinil or placebo) in a 1:1 ratio. Subjects will be stratified based on Baseline 6MWD (≤350 meters versus >350 meters).

Subjects will be treated with either inhaled treprostinil (6 mcg/breath) or placebo.

The study will consist of the following phases:

Screening Phase: Prospective subjects will undergo a screening evaluation within 30 days prior to the Baseline Visit (randomization and first dose of study drug). During this phase, eligible subjects will sign the informed consent form (ICF) and undergo Screening assessments. The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline pulmonary function tests (PFTs) and 6-Minute Walk Test (6MWT) used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Baseline Visit: The Baseline assessments may be conducted over a 48-hour period prior to the first dose of study drug to allow for scheduling of all activities. Eligible subjects will undergo Baseline assessments, be assigned to a treatment group based on the randomization schedule, and receive the first dose of study drug (Day 1 is defined as the day the first dose of study drug is given). The Screening and Baseline assessments may be combined if all entry criteria are satisfied within 48 hours prior to the first dose of study drug. Baseline PFTs and 6MWT used to confirm eligibility criteria may be performed on the same day but prior to the first dose of study drug.

Treatment Phase: The Treatment phase consists of 5 study visits to the clinic at Week 4, Week 8, Week 12, Week 15, and Week 16 (final study visit; at least 24 hours after the Week 15 Visit [final study visit/early termination {ET}]). Subjects will also be contacted at least weekly by telephone or email to assess subject tolerance to study drug, AEs, and changes to concomitant medications.

4 SEQUENCE OF PLANNED ANALYSES

Interim Safety Analyses

Interim safety analyses are intended to be performed according to the Data Monitoring Committee (DMC) Charter. In particular, interim safety analyses are planned following the enrollment of approximately 25%, 50%, and 75% of subjects in the study, or at least annually (whichever is sooner). All analyses will be prepared by an independent external consultant and reviewed only by the independent DMC as defined in the DMC Charter. The Sponsor will only have access to the blinded study data during this process. Interim efficacy analyses are not planned in this study.

Dry-run Analysis Prior to Database Lock (Soft Lock)

At the completion of the study enrollment and prior to the database lock, a dry-run analysis is planned. This dry-run analysis utilizes a dummy randomization schedule in a blinded fashion. The purpose of the dry-run analysis is to verify programming of the analysis data sets and the planned tables, listings, and figures, and to identify any data issues. Programming and data issues identified through the dry-run process will be resolved prior to the database lock and study unblinding.

Final Analysis after Database Lock and Study Unblinding

After the database has been quality assured and locked, the treatment assignments will be provided to the sponsor's project statistician by the central randomization service and all planned analyses described in this document will be performed. By intent, no changes will be made to the clinical database after unblinding. However, any changes that are deemed necessary, after unblinding, will be clearly documented in the CSR.

5 SAMPLE SIZE CONSIDERATIONS

Using an allocation ratio of 1:1 between inhaled treprostinil and placebo, a sample size of approximately 266 subjects (133 per treatment) would provide at least 90% power at a significance level of 0.05 (2-sided hypothesis) to detect a 30 meter between-treatment difference in the change from Baseline to Week 16 in 6MWD, assuming a standard deviation of 75 meters.

The total sample size will be approximately 314 subjects to account for a discontinuation rate of approximately 15%.

6 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population is defined as all subjects randomized into the study who received at least 1 dose of study drug. All ITT subjects will be counted in the group to which they were randomized, regardless of the study drug they were given. All efficacy analyses will be performed on this ITT population, unless otherwise specified.

The Safety population is defined as all subjects enrolled into the study who received at least 1 dose of study drug. All Safety population subjects will be counted in the group corresponding to the study drug received, regardless of randomized assignment. All safety analyses will be performed on this Safety population, unless otherwise specified.

The Per-protocol population will include all subjects in ITT population, excluding subjects with major protocol deviations that may have an impact on the primary efficacy analyses. The major protocol deviations and the subject's exclusion from the Per-protocol population will be reviewed at a blinded data review meeting and documented prior to the database lock and the study unblinding.

7 INTERIM ANALYSES

There is no interim efficacy analysis for this study.

A DMC will be established for the study including physicians knowledgeable in the treatment of PH and a statistician. Throughout the course of the study the DMC will meet on a regular basis to monitor the safety of the study. Meetings will occur as outlined in the DMC Charter. All analyses will be prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC Charter. The Sponsor will only have access to blinded study data during this process. The details regarding the interim safety analysis will be included in a separate SAP.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All the data collected in the electronic Case Report Form (eCRF) will be listed. In general, listings will be sorted by treatment group, subject number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), study day, and all relevant data collected in the eCRFs. For data collected on a fixed schedule, the assessment identifier or the nominal time point will also be included on the listing. Repeat or redundant observations within an assessment window and observations that do not fall within any predefined assessment window (and will, therefore, be excluded from summaries) will be flagged in these listings. Subjects who are not to be included in the analysis population (eg, Safety population, Per-protocol population) will be flagged.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group. For continuous variables, summary statistics will include the mean, standard deviation, median, minimum, and maximum. For summaries of non-normal data such as 6MWD, interquartile range (lower quartile, upper quartile) may also be included. Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal place than was collected. For discrete variables, summaries will include the frequency and percentage in each category. Percentages will be rounded to 1 decimal place. For all inferential analyses and descriptive comparisons, p-values will be rounded to 4 decimal places. Values less than 0.0001 will be denoted as <0.0001, and values greater than 0.9999 will be denoted as >0.9999 whenever practical, categories of discrete variables will be ordered and labelled as they appear in the eCRF, and all categories represented on the case report form will be included in summaries, even when they do not apply to any subjects in the study.

Unless otherwise specified, all statistical tests will be 2-sided at alpha level 0.05. All statistical calculations will be completed using SAS® Version 9.4 or above.

8.1 COVARIATES

The primary efficacy analyses of change in 6MWD at Week 16 will be adjusted for Baseline 6MWD (as a continuous variable). For sensitivity analyses of the primary efficacy endpoints

and the secondary/exploratory endpoints with continuous variables, the baseline measure will always be the covariate.

8.2 EXAMINATION OF SUBGROUPS

For primary efficacy endpoints of change in 6MWD at Week 16, subgroup analyses will be performed. These subgroups will include:

- Etiology of ILD (Idiopathic Interstitial Pneumonia [IIP], Chronic Hypersensitivity Pneumonitis [CHP], Occupational, CPFE, Connective Tissue Disease [CTD], and Other)
- Baseline walk categories (≤350 meters versus >350 meters, ≤ median baseline 6MWD versus > median baseline 6MWD)
- ILD disease severity as measured by Baseline DLCO (<40% predicted versus ≥40% predicted)
- Sex (male versus female)
- Pulmonary Vascular Resistance (PVR) (<4 versus ≥4 Wood Units [WU])
- Age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths)

No Type 1 error adjustments will be performed for these subgroup analyses.

8.3 PREMATURE DISCONTINUATION AND MISSING DATA

8.3.1 Missing Data Handling for 6MWD

For the analysis of 6MWD, subjects may not have completed the treatment with study drug prior to the Week 16 visit for the following reasons: death, progressive disease, AE, withdrawal of consent by the subject, protocol violation, loss to follow-up, termination of study by the sponsor, or withdrawal for other reasons. Every attempt must be made to perform all efficacy assessments immediately prior to premature termination of study drug or withdrawal from the study. In addition, subjects still receiving study drug may be too critically ill to perform the 6MWT, resulting in missing data for that assessment.

Every effort should be made to complete all scheduled study assessments for all randomized subjects. Although attempts will be made to continue to collect data after termination of study drug, these data are being collected for sensitivity analyses and descriptive purposes

only. Assessments performed after treatment unblinding or more than 24 hours after the last dose of study drug will not be included in the main analyses of peak 6MWD.

For subjects whose peak 6MWD measures at Week 4, Week 8, Week 12, or Week 16 are missing, the missing value will be imputed as described in Table 8-1.

Table 8-1 Imputation Rules for Peak 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening event	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Last (peak) Observation Carried Forward (LOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test

For subjects whose trough 6MWD measures at Week 15 are missing, the missing values will be imputed as described in Table 8-2.

Table 8-2 Imputation Rules for Trough 6MWD

Reason for missing 6MWD measure	Imputation
Death (all causes)	Worst score (0 meters)
Clinical worsening	Worst score (0 meters)
Too ill to perform 6MWT	Worst score (0 meters)
All other reasons	Baseline Observation Carried Forward (BOCF)

Abbreviations: 6MWD, 6-Minute Walk Distance; 6MWT, 6-Minute Walk Test

8.3.2 Missing Data Handling for Other Efficacy Assessments

For the secondary endpoints of NT-proBNP, the missing value at Week 16 will be imputed using LOCF. If the NT-proBNP measure at Baseline is missing, the change from Baseline will not be calculated. The subject will not be included in the analyses.

For exploratory endpoints of SGRQ, biomarkers, and DSP, the missing values will not be imputed, and all analyses will be based on the observed cases.

8.4 MULTIPLE COMPARISONS AND MULTIPLICITY

The primary efficacy endpoint of change in 6MWD measured at peak exposure from Baseline to Week 16 will be tested at alpha level 0.05. If the primary efficacy endpoint is statistically

significant at alpha level 0.05, the statistical tests for secondary efficacy endpoints will be performed.

To control the Type 1 error rate, the secondary efficacy endpoints will be tested using a hierarchical (fixed sequence) testing procedure. The secondary endpoints will be tested in the following order:

1. Change from Baseline in plasma concentration of NT-proBNP at Week 16
2. Time to clinical worsening
3. Change from Baseline in peak 6MWD at Week 12
4. Change from Baseline in trough 6MWD at Week 15

Testing will proceed only if the preceding test is statistically significant at 2-sided alpha level equal to 0.05 and will stop if non-significance is reached.

8.5 DERIVED AND TRANSFORMED DATA

Time to clinical worsening will be evaluated as a secondary endpoint and calculated as the time from randomization until 1 of the following criteria are met:

- Hospitalization due to a cardiopulmonary indication
- Decrease in 6MWD >15% from Baseline directly related to disease under study at 2 consecutive visits and at least 24 hours apart
- Death (all causes)
- Lung transplantation

Time to clinical worsening is calculated as described in Table 8-3.

Table 8-3 Derivation of Time to Clinical Worsening

Parameter	Scenario	Formula	Status
Time to clinical worsening (weeks)	Subjects with clinical worsening event reported	= (Worsening date – Randomization date +1)/7	0 (event)
	Subjects who died during the study	= (Death date – Randomization date +1)/7	0 (event)
	Subjects without clinical worsening event during the study	= (Last assessment date – Randomization date +1)/7	1 (censored)
	Subjects discontinued from the study prematurely	= (Last assessment date – Randomization date +1)/7	1 (censored)

For subjects with clinical worsening due to decrease from Baseline in 6MWD, a confirmatory 6MWT should be conducted. The event time is based on the date of the confirmatory 6MWT. If the confirmatory 6MWT is not conducted, the event time is then based on the date of the first 6MWT.

Distance Saturation Product (DSP) is calculated as follows:

Parameter	Formula
DSP (m%)	= (Distance walked in meters) x (Lowest oxygen saturation recorded during the 6MWT)

Abbreviations: 6MWT, 6-Minute Walk Test; DSP, Distance Saturation Product

Adjustments to the QT intervals will be calculated as follows:

Parameter	Formula
QTc (Bazett)	$= \text{Q-T}/\sqrt{60/\text{HR}}$
QTc (Fridericia)	$= \text{Q-T}/\sqrt[3]{60/\text{HR}}$

Abbreviations: HR, Heart rate; QTc, Q-T interval corrected for heart rate; Q-T, Electrocardiographic interval from beginning of QRS complex to end of the T wave

8.6 ASSESSMENT WINDOWS

For any data summarized by scheduled visit, an analysis visit window will be used. The scheduled visits, as recorded on the eCRFs, and the corresponding target days and study day intervals are specified in Table 8-4. The analysis visit window will be derived based on the information specified in Table 8-4.

In the protocol, the visit window for Week 4, Week 8, Week 12, and Week 16 is ±5 days and the visit window for the Week 15 visit is ±5 days and at least 24 hours prior to Week 16 6MWT. In order to allow slotting of discontinuation visits and visits outside the planned schedule, the visit windows have been expanded for analysis purposes for Week 4, Week 8, Week 12, and Week 16. The nominal study visit identified as Week 15 in the eCRF will be used for the Week 15 visit.

Table 8-4 Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
ECGs, SGRQ:		
Baseline	1	Study Day ≤1 (prior to the date of the first dose)
Week 16	113	1 < Study Day
PFTs, Clinical laboratory assessments and NT-proBNP:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 8	57	1 < Study Day ≤ 84
Week 16	113	84 < Study Day
Peak 6MWT:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 16	113	99 < Study Day
Trough 6MWT:		
Week 15	106	Nominal study visit

Visit	Target Study Day	Study Day Interval
Vital signs, Pulse oximetry:		
Baseline	1	Study Day ≤1 (prior to the first dose)
Week 4	29	1 < Study Day ≤ 43
Week 8	57	43 < Study Day ≤ 71
Week 12	85	71 < Study Day ≤ 99
Week 15	106	Nominal study visit
Week 16	113	99 < Study Day

Abbreviations: 6MWT, 6-Minute Walk Test; ECG, Electrocardiogram; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PFT, Pulmonary function test, SGRQ, St. George's Respiratory Questionnaire
Note: Study Day = (Assessment Date) − (First Dosing Date) +1

Multiple Evaluations within the Same Analysis Window

After all the observations have been slotted based on the table above, if there are multiple valid observations for an assessment within an assigned analysis visit window, only 1 of these observations will be used for summary statistics and analyses. The observation to be used is determined using the following hierarchy (in decreasing order):

- The observation closest to the target study day
- The later observation if 2 observations are equally close to the target study day

For missing values where the LOCF algorithm is applied, it is always the last valid observation on treatment carried forward, even though this might not be the observation obtained by the above hierarchy and used in the summaries by visit window.

9 STUDY POPULATION

Unless otherwise specified, all efficacy analyses will be performed on the ITT population and all safety analyses will be based on the Safety population. In the ITT population, the treatment assignment is based on the assignment upon randomization. In the Safety population, the treatment assignment is based on the actual treatment the subject received.

The comparability between the 2 treatment groups will be checked for demographic and baseline characteristics. The p-values from Fisher's exact test (for discrete variables) or Group t-test or Wilcoxon rank sum test (for continuous variables) will be included on

summaries but are not intended to be used to test formal hypotheses. For these comparisons, missing or unknown values will be excluded from the calculations.

9.1 SUBJECT ACCOUNTABILITY

All subjects' disposition information will be listed by individual subject number, including the analysis population the subjects belong to, premature study drug discontinuation status, primary reason for premature study drug discontinuation, premature study discontinuation status, primary reason for premature study discontinuation, number of days on the study drug, and enrollment in the open label extension study (RIN-PH-202).

The listing of subject accountability will include the dates of informed consent and randomization, the first study drug dose, last study drug dose, and last assessment dates and times, and the last dose and assessment weeks. Whether subjects received the study drug, whether subjects completed the Weeks 4, 8, 12, 15, 16 assessments, and study discontinuation status will be summarized.

Information regarding whether each subject is included in each analysis population (see Section 6) will be listed. If a subject is not included in a particular analysis population, the reason for exclusion will be noted on the listing. Also noted on the listing will be the randomized treatment assignment and the actual treatment subjects have received. The summary will include the frequency and percentage of all subjects in each analysis population.

The stratification information used in the random assignment of subjects to treatment group (from the central randomization database) will be listed, including date and time of randomization and Baseline 6MWD category (≤350 meters versus >350 meters). Status of the treatment blind, and if broken, date/time of blind broken will be listed. The number of subjects in each stratum will be summarized by treatment group and overall.

9.2 PROTOCOL DEVIATIONS

The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment, whether all eligibility criteria were met (Yes/No), and a list of any specific entry criteria not met. This listing will also include the protocol version that the subject was enrolled under. Entry criteria violations will be summarized by treatment group and overall.

Additional protocol deviations will be documented throughout the study. All deviations will be reviewed by the clinical team prior to database lock and those that might affect subject safety or efficacy outcomes will be considered ‘Major’. All other deviations will be classified as ‘Minor’. Protocol deviations will be listed, including the date of the deviation, the type of deviation, the severity of the deviation (Major/Minor), and a description of the deviation. The protocol deviations will also be summarized by treatment group and overall.

9.3 OTHER DESCRIPTIONS OF STUDY POPULATION

9.3.1 Demographics

All demographic data will be listed for all subjects, including assessment date, date of birth, country, age, sex, ethnicity, race, weight, height, and body mass index (BMI). Age, age category (<65 years of age, 65 to <80 years of age, and ≥80 years of age), sex, ethnicity, race, height, weight, and BMI will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher’s exact test (for age category, sex, ethnicity, and race) and group t-test or Wilcoxon rank sum test (for age, weight, height, and BMI) comparing treatment groups.

9.3.2 Baseline Characteristics

Baseline characteristics will include the Baseline 6MWD, Baseline NT-proBNP, and hemodynamic parameters. Hemodynamic parameters, measured by the right heart catheterization (RHC), will include PVR, pulmonary artery pressure mean (PAPm), pulmonary capillary wedge pressure (PCWP), and details concerning vasodilator testing will be listed and summarized.

9.3.3 Medical History and PH-ILD History

All significant past or ongoing medical conditions will be listed for all subjects. The listing will include the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for each condition listed, and whether the condition is ongoing at Randomization. These medical conditions will be summarized by PT within each SOC.

Information related to subjects' PH-ILD history will be listed. The listing will include the date of initial PH diagnosis, years since PH diagnosis, etiology of ILD (including IIP subcategory), date of confirmatory computed tomography (CT) scan, whether ILD diagnosis confirmed with a lung biopsy, and if so, the date of lung biopsy.

The current ILD diagnosis (ILD category) and IIP subcategory, time since PH diagnosis, and whether ILD diagnosis was confirmed via lung biopsy will be summarized by treatment group and overall. The summary will include p-values (2-sided) from Fisher's exact test (for current ILD diagnosis) or Wilcoxon rank sum test (for time since diagnosis) comparing treatment groups.

9.3.4 Concomitant Medications

All concomitant medications recorded on the eCRF will be mapped to a standard name and Anatomical Therapeutic Chemical (ATC) Levels 1 to 4 using the World Health Organization (WHO) WHODrug Global drug dictionary. The ATC Levels 2 and 4 and verbatim term of all concomitant medications will be listed for all subjects. This listing will include the date started (or indication that drug was ongoing at randomization), date discontinued (or indication that drug was ongoing at end of study), and the condition(s) treated/indication(s). Summary of concomitant medications present at Baseline and summary of concomitant medications added during the study will include the frequency and percentage of subjects in each treatment group receiving each drug by ATC Level 2 and Level 4. If ATC Level 4 is not available for a medication, ATC Level 3 will be substituted. If ATC Level 3 is not available, ATC Level 2 will be substituted. If ATC Level 2 is not available, ATC Level 1 will be substituted.

10 EFFICACY ANALYSES

Except where otherwise noted, all efficacy analyses will only be performed on the ITT population (see Section 6).

10.1 PRIMARY EFFICACY MEASURES

10.1.1 Primary Efficacy Analyses

10.1.1.1 Hypothesis

The primary efficacy endpoint of peak 6MWD assesses if inhaled treprostinil will increase the distance traversed in the peak 6MWT at Week 16 over placebo in subjects with PH-ILD. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2,$$

where μ_1 and μ_2 are the median change from Baseline in 6MWD of the inhaled treprostinil and placebo treatment groups, respectively.

10.1.1.2 Primary Efficacy Analysis

All 6MWT data will be listed for all subjects. For each scheduled assessment, this listing will include the date test was performed (or date test was intended to be performed if subject is unable to attempt the test), start time of the test, nominal time point, last treatment dose, hours from last treatment dose to 6MWT start, if walk was attempted, total distance walked (in meters), whether subject received oxygen during the test, amount of supplemental oxygen, and any circumstances that adversely affected the walk (if any) including reason for not attempting test (if any). The trough 6MWT measure will also be indicated. In addition, a listing of 6MWD with imputed values will be included for both peak and trough 6MWD data.

For the primary efficacy analysis, the effect of inhaled treprostinil versus placebo on change in peak 6MWD at Week 16 will be evaluated via analysis of covariance (ANCOVA). Change from Baseline in peak 6MWD is the dependent variable, and treatment and Baseline 6MWD are covariates in this ANCOVA model. Least squares means and standard errors for each treatment group, the least squares mean difference and its standard error, as well as a 95% confidence interval for the treatment group difference and p-value for treatment group

comparison will be calculated from the ANCOVA model. This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. The LOCF algorithm will be applied.
4. ANCOVA will be conducted based on the pseudo SAS code:

```
proc glm;
  class Treatment;
  model DistC = Treatment Dist0;
run;
```

where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.

If the ANCOVA assumptions are violated, the primary efficacy analysis will be based on non-parametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (Koch 1990, Koch 1998, Stokes 2000). Specifically, a Cochran-Mantel-Haenszel mean score test will be used on the standardized mid-ranks (ie, overall rank divided by the number of ranks +1, or “modified ridit” scores) of the residuals from an ordinary least squares regression with change from Baseline in peak 6MWD at Week 16 as a linear function of distance walked at Baseline (as a continuous variable). This methodology will be carried out as follows:

1. Walk distances obtained after study drug termination or unblinding will be excluded (as described in Section 8).
2. Imputation rules in Table 8-1 will be applied.
3. Calculate ranks. The pseudo SAS code is as follows:

   ```
   proc rank nplus1 ties=mean out=ranks;
     var DistC Dist0;
   run;
   ```

   where DistC is the change from Baseline in peak 6MWD at Week 16 and Dist0 is the baseline measure of the 6MWD.
4. Linear regression model will be fit using the rank values generated above. The pseudo SAS code is as follows:

```
proc reg data=ranks noprint;
  model DistC=Dist0;
  output out=residual r=resid;
run;
```

where DistC is the rank value of the change from Baseline in peak 6MWD at Week 16 and Dist0 is the rank value of the baseline measure of the 6MWD.

5. A mean score test, using the values of the residuals as scores, compares the treatment groups. Cochran-Mantel-Haenszel mean score statistic and p-value will be calculated, using the NOPRINT and CMH2 options in the TABLES statement of the FREQ procedure of SAS. The pseudo SAS code is as follows:

```
proc freq data=residual;
  tables Treatment*Resid / noprint cmh2;
run;
```

where Treatment indicates the randomized treatment group, and Resid represents the residuals obtained from the above linear regression models.

In addition to the p-value from the non-parametric method described above, the Wilcoxon rank sum test and the Hodges-Lehmann estimate of median difference (as an estimate of location shift between 2 treatment groups for the placebo-controlled treatment effect) will be provided. The Wilcoxon rank sum test and the Hodges-Lehmann estimate can be obtained through the following pseudo SAS code:

```
proc npar1way hl Wilcoxon;
   class treatment;
   var DistC;
run;
```

where DistC is the change from Baseline in peak 6MWD at Week 16.

10.1.1.3 Sensitivity and Subgroup Analyses

In order to analyze walk distances at each scheduled assessment, values for missing or excluded assessments up to and including Week 16 will be imputed according to rules described in Section 8.3.1.

To further support the robustness and assess the sensitivity of the primary efficacy analysis of change in peak 6MWD at Week 16 (provided that the primary analysis yields significant

results), the above non-parametric and parametric analyses and summaries will be repeated using each of the following modifications (as data permit):

- The Per-protocol population will be used instead of the ITT population
- Missing data imputation using the LOCF method (based on peak values)
- Missing data imputation using the last rank carried forward (LRCF) method (based on peak values) (O'Brien 2005)
- Using only the observed values without imputation
- Including data collected after termination of the study drug
- ITT population excluding subjects with a reported exacerbation within 3 days of the Week 16 peak 6MWT measure
- Stratified by ILD etiology categories (IIP, CHP, Occupational, CPFE, and Other)
- Stratified by Baseline 6MWD categories (≤350 meters versus >350 meters, ≤median baseline 6MWD versus > median baseline 6MWD)
- Stratified by Baseline DLCO percent predicted (<40% versus ≥40%)
- Stratified by Baseline pulmonary vascular resistance (PVR) (<4 versus ≥4 WU)
- Stratified by sex (male versus female)
- Stratified by age group (<65 years of age, 65 to <80 years of age, and ≥80 years of age)
- Stratified by study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths).

A longitudinal data analysis using mixed model repeated measurement (MMRM) will also be performed to estimate the treatment difference in change in peak 6MWD at Week 16. The MMRM will include the change from Baseline in peak 6MWD as the dependent variable, treatment, week, and treatment by week interaction as fixed effects, and Baseline 6MWD as a covariate. An unstructured variance/covariance structure shared across treatment groups will be used to model the within-subject errors.

Additional sensitivity analyses on the ITT and Per-protocol populations for change from Baseline to Week 16 in peak 6MWD will be based on a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model will include treatment group, all scheduled visits (Baseline and Weeks 4, 8, 12, and 16), subject's sex, and subject's age at randomization.

An additional sensitivity analysis will be performed for percent change from Baseline to Week 16 in peak 6MWD using the same approach as the primary analysis method where the percent change from Baseline is calculated as

$$\frac{\text{peak 6MWD at Week 16} - \text{Baseline 6MWD}}{\text{Baseline 6MWD}} \text{X } (100\%).$$

In addition, the impact of Baseline hemodynamics and Baseline PFTs, including PVR, PAPm, PCWP, FEV_1, FVC, TLC, and DLCO as continuous variables, on peak 6MWD, will be explored using the regression approach.

Finally, to determine whether site has an effect on treatment estimates, site will be added to the ANCOVA model in Section 10.1.1.2 as a random effect. If necessary, sites with small numbers of subjects may be pooled.

10.2 SECONDARY EFFICACY MEASURES

Secondary efficacy endpoints include the following:

- Change in plasma concentration of NT-proBNP from Baseline to Week 16
- Time to clinical worsening calculated as the time from randomization until 1 of the following criteria are met:
  a. Hospitalization due to a cardiopulmonary indication
  b. Decrease in 6MWD >15% from Baseline directly related to disease under study, at 2 consecutive visits and at least 24 hours apart
  c. Death (all causes)
  d. Lung transplantation
- Change in peak 6MWD from Baseline to Week 12
- Change in trough 6MWD from Baseline to Week 15

As specified in Section 8.4 above, the hierarchical (fixed-sequence) testing procedure will be employed to control the overall alpha level at 0.05.

10.2.1 Change in NT-proBNP at Week 16

The efficacy endpoint of the change in NT-proBNP plasma concentration assesses if inhaled treprostinil decreases the level of NT-proBNP at Week 16 over placebo in subjects with PH-ILD. The null and alternative hypotheses are:

$$H_0: \mu_1 = \mu_2$$
$$H_a: \mu_1 \neq \mu_2,$$

where μ_1 and μ_2 are the mean changes from Baseline to Week 16 in log-transformed NT-proBNP of the inhaled treprostinil and placebo treatment groups, respectively, and change from Baseline is calculated as log(value at Week 16) – log(value at Baseline).

The NT-proBNP values will be listed for all subjects, including the nominal time point, collection date/time, normal range and "High/Low" flag. The values and their respective changes from Baseline will be summarized for each assessment. The summary will also include the geometric mean and geometric standard deviation. The difference between treatment groups for the change from Baseline to Week 16 will be tested using the analysis of covariance with change from Baseline in log-transformed NT-proBNP as the dependent variable, treatment as the fixed effect, and Baseline log-transformed NT-proBNP as the covariate. The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model BNP_C=Treatment BNP_B;
run;
```

where BNP_C is the change from Baseline to Week 16 in log-transformed NT-proBNP and BNP_B is the log-transformed NT-proBNP at Baseline.

For subjects who do not have NT-proBNP measurements at Week 16, the LOCF imputation will be used. The analyses will also be performed for the data without imputation for the missing measures.

As an exploratory analysis, the NT-proBNP at Week 8 will be analyzed using the same method as the NT-proBNP at Week 16.

A longitudinal data analysis using MMRM will also be performed to estimate the treatment difference in changes from Baseline for log-transformed data in NT-proBNP. The MMRM will include log-transformed NT-proBNP as the dependent variable; treatment, week, and

treatment by week interaction as fixed effects; and Baseline log-transformed NT-proBNP as a covariate. An unstructured variance/covariance structure shared across treatment groups will be used to model the within-subject errors and the Kenward-Roger method will be used for calculating the denominator degrees of freedom. The appropriate contrasts will be constructed in order to estimate treatment effect at Weeks 8 and 16.

10.2.2 Time to Clinical Worsening

Data on the clinical worsening assessment page of the eCRF will be used to determine clinical worsening status. Investigator-reported clinical worsening events including the date (study day) of the event, category of the clinical worsening event, Baseline 6MWD, first 6MWT details, and second 6MWT details will be listed. The time to clinical worsening will be calculated according to the rules described in Table 8-3 in Section 8.5.

The number and percentage of subjects with any clinical worsening and with each category of clinical worsening will be summarized by treatment group. Time to clinical worsening will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. A tabular summary of this analysis will include the number of subjects at risk (sample size), estimated median duration, and a 95% confidence interval for the median duration for each treatment group. The log-rank test, adjusted for Baseline 6MWD category, will be used to calculate the p-value for treatment differences in the ITT population.

The SAS Procedure LIFETEST will be used. The pseudo SAS statements are listed below:

```
proc lifetest;
  time TimeToWorsening*Censor_Status(1);
  strata B_6MWD / group = Treatment test=all;
run;
```

where B_6MWD denotes the categorical Baseline 6MWD variable (≤350 meters versus >350 meters).

In addition, the Cox proportional hazards model will be fit to obtain the hazard ratio and its associated 95% confidence interval. The model will include treatment and Baseline 6MWD as explanatory variables. The SAS procedure PHREG will be used. The pseudo SAS statements are listed below:

```
proc phreg;
  class Treatment;
  model TimeToWorsening*Censor_Status(1) = Treatment Dist0
        / risklimits alpha=0.05 ties=efron;
  assess var=Dist0 ph;
run;
```

where Dist0 denotes the Baseline 6MWD variable (continuous). If it is determined that the proportional hazards assumption does not hold for Baseline 6MWD, a stratified analysis will be conducted. The above SAS code will be amended to remove Dist0 from the model statement and add the 'strata B_6MWD;' statement.

If the proportional hazards assumption does not hold for the Cox model, the restricted mean survival time (RMST) and its associated standard error will be calculated for each treatment group at Week 16 (Royston 2013). A 95% confidence interval will be constructed for the difference in RMST between the 2 treatment groups at Week 16.

10.2.3 Change in Peak 6MWD at Week 12

The methodology for primary efficacy analysis of change in peak 6MWD at Week 16 will also be carried out for the Week 12 assessment, as described above in Section 10.1.1.2.

10.2.4 Change in Trough 6MWD at Week 15

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the change in trough 6MWD from Baseline to Week 15. Missing trough 6MWD will be imputed as described in Table 8-2 in Section 8.3.1. The analysis will be repeated to include only subjects with trough 6MWD at Week 15 (ie, missing trough 6MWD at Week 15 is not imputed).

10.3 EXPLORATORY EFFICACY MEASURES

Exploratory efficacy endpoints include the following parameters:

- Change in peak 6MWD from Baseline to Week 4
- Change in peak 6MWD from Baseline to Week 8
- Change in quality of life as measured by SGRQ from Baseline to Week 16
- Change in DSP from Baseline to Week 16

10.3.1 Change in Peak 6MWD at Weeks 4 and 8

The methodology for primary efficacy analysis of change in peak 6MWD described in Section 10.1.1.2 will also be carried out for the assessments obtained at Week 4 and Week 8.

10.3.2 Change in SGRQ at Week 16

The responses to the SGRQ questionnaire at Baseline and Week 16 will be converted to the Total score and 3 domain scores according to the SGRQ manual (Jones 2002). Scores for Total and each domain will range from 0 to 100, with higher scores indicating more limitations. Both individual item responses as well as calculated scores will be listed. The change from Baseline for the Total and 3 domain scores (Symptoms, Activity, and Impacts) will be calculated.

The Total score and for the 3 domain scores as well as their changes from Baseline will be summarized by treatment group using descriptive statistics.

For the Total score and each of the 3 domain scores, treatment differences (inhaled treprostinil vs. placebo) will be tested by using analysis of covariance with change from Baseline as the dependent variable, treatment as a fixed effect, and baseline score as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model Score_C=Treatment Score_B;
run;
```

where Score_C is the change from Baseline in Total score or each of the 3 domain scores and Score_B is the corresponding score at Baseline.

10.3.3 Change in DSP

The DSP will be calculated, and DSP results will be included in the data listing for pulse oximetry. DSP values and their respective changes from Baseline to Week 16 will be summarized by treatment group. The difference between treatment groups for the change from Baseline to Week 16 will be tested using analysis of covariance with change from Baseline in DSP as the dependent variable, treatment as a fixed effect, and Baseline DSP measure as the covariate. The analyses will be based on the observed data with no imputation.

The pseudo SAS code is as follows:

```
proc glm;
  class treatment;
  model DSP_C=Treatment DSP_B;
run;
```

where DSP_C is the change from Baseline to Week 16 in DSP (m%) and DSP_B is DSP at Baseline.

In addition, the DSP at Week 4, Week 8, and Week 12 will each be analyzed in the same way as the DSP at Week 16.

11 HEALTH OUTCOMES

11.1 QUALITY OF LIFE MEASURES

Quality of life was assessed using SGRQ. The analyses of SGRQ are described in Section 10.3.2.

11.2 RESOURCE UTILIZATION MEASURES

Hospitalizations and hospitalizations related to cardiopulmonary indications are collected during the study. The analysis is discussed in Section 12.6.2.

12 SAFETY ANALYSES

All safety analyses will be performed only on the Safety population (see Section 6).

12.1 EXTENT OF EXPOSURE

All study drug dosing will be listed for all subjects. The listing will include initial dose (number of breaths for each session and number of breaths for the day) and date of this initial dose and dose and date of each subsequent dose change. Dosing at Weeks 4, 8, 12, 15, and 16 will be summarized for subjects still receiving study drug at each of these assessments. The summary will include both the numeric summaries and the categorical summaries for number of breaths per session as well as the number of breaths per day. If study drug is dosed differently across different sessions on the same day, the maximum number of breaths is used for summarization. Summary of overall duration of exposure will be included as well as the final dose (breath/session) and the maximum study drug dose (breath/session) reached for each subject (numerically and categorically).

For study treatment compliance, the number and percentage of days with dose >0 breaths will be calculated and summarized.

12.2 ADVERSE EVENTS

All AEs will be coded to the appropriate PT and SOC using MedDRA. AEs will be listed by treatment group including all details recorded on the eCRF plus an indicator of whether the event was treatment-emergent. The AE listings will include the AE verbatim term and its corresponding PT and SOC.

The AE summaries will be limited to include only treatment-emergent AEs. Treatment-emergent AEs are those AEs with onset date equal to or after the start date of the study drug. The non-treatment-emergent AEs (the AEs occur after signing the informed consent form but before receiving study drug) will be listed but not included in summary tables.

All summaries will include the number and percentage of subjects experiencing each type of adverse event and the total number of each type of adverse event, in order of overall frequency and/or SOC. Serious adverse events (SAE) and non-serious AEs will also be summarized by SOC and PT.

The total number of AEs and the AE rates will be calculated and summarized for each display, as appropriate. The AE rate will be calculated as the total number of AEs divided by the total patient years of exposure to study drug per treatment group.

Adverse events possibly or probably related to study drug will be summarized. An AE summary by severity (mild, moderate, and severe) will also be provided.

Separate listings and summary tables will be provided for all SAEs, AEs leading to the discontinuation of study drug, and all deaths during the study (if data permit). For listing of deaths, information for all subjects who die during the study period from the randomization to the end of study (including 30 days after the last study treatment dosing) will be included.

12.3 OXYGENATION

Oxygenation is measured by pulse oximetry (SpO_2 and supplemental oxygen requirement [L/min]) during each 6MWT. At each 6MWT, pulse oximetry (for SpO_2) will be measured at pre-walk, during walk, and post-walk. During walk, the lowest SpO_2 will be recorded. All pulse oximetry results along with the collection date/time (study day) will be listed. Heart rate will be listed for pre-walk and post-walk only.

The SpO_2 will be summarized by treatment group, visit, and time point (pre-walk, during walk, and post-walk). The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from Baseline calculations, the measurements pre-walk, during walk, and post walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk, during walk, and post-walk at Baseline.

In addition, for each time point at each visit, the number and percentage of subjects with SpO_2 or lowest SpO_2 <80%, ≥80 to <88, and ≥88%, and with SpO_2 dropping ≥10% during walk and/or post-walk from pre-walk will be summarized by treatment group.

At each visit, supplemental oxygen requirements will be collected at rest and during 6MWT. These data will be listed, including visit, 6MWT date/time, and oxygen use at rest and during walk. The number and percentage of subjects requiring supplemental oxygen use at rest and

during the 6MWT will also be summarized by the treatment group. Supplemental oxygen level at rest at each visit and the corresponding changes from Baseline will be summarized by treatment group.

Heart rate will be summarized by treatment group, by time point (pre-walk and post-walk) and visit. The summary will be provided for the original values, change from pre-walk for each visit, and change from baseline values. For change from baseline calculations, the measurements pre-walk and post-walk at post-Baseline Visits will be compared with the measurements at corresponding pre-walk and post-walk at Baseline.

12.4 PULMONARY FUNCTION TESTS

The PFT parameters include:

- Forced expiratory volume in 1 second (FEV_1)
- Forced vital capacity (FVC)
- Total lung capacity (TLC)
- Lung diffusion capacity (DLCO)

Only pre-bronchodilator values will be recorded on eCRF and will be listed. All PFT parameters and their change from baseline values will be summarized by treatment group and visit.

For FEV_1 results, the number and percentage of subjects with FEV_1 decreasing more than 20% from Baseline at any post-Baseline Visit will be summarized by treatment group.

12.5 CLINICAL LABORATORY EVALUATIONS

Blood samples will be taken at Screening and/or Baseline, Week 8, and Week 16. All samples will be sent to a central laboratory for evaluation of clinical chemistry and hematology.

12.5.1 Clinical Chemistry

The following clinical chemistry parameters will be evaluated by the central laboratory:

Parameter	Units
Sodium	mmol/L
Potassium	mmol/L
Bicarbonate	mmol/L
Chloride	mmol/L
Total bilirubin	umol/dL
Alkaline phosphatase	U/L
Alanine aminotrasferase	U/L
Aspartate aminotransferase	U/L
Urea nitrogen	mmol/dL
Creatinine	umol/L
Calcium	mmol/L
Albumin	g/L

Values that are “High” or “Low” with respect to the reference range provided by the central laboratory will be flagged with an “H” or an “L,” respectively. All parameters will be listed for all subjects and assessments, along with their respective “High/Low” flags.

Values of these parameters at each visit, and their corresponding changes from Baseline will be descriptively summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who had “Low,” “Normal,” or “High” Baseline values, then subsequently had “Low,” “Normal,” or “High” follow-up values at each visit will be presented in a shift summary.

12.5.2 Hematology

The following hematology parameters will be evaluated by the central laboratory:

Parameter	Units
Hemoglobin	g/dL
Hematocrit	%
Red blood cell count	10^6/uL
Red blood cell morphology	
White blood cell count	10^3/uL
Platelet count	10^3/uL

Values that are "High" or "Low" with respect to the reference range provided by the central laboratory will be flagged with an "H" or an "L," respectively. All parameters will be listed for all subjects and assessments, along with their respective "High/Low" flags.

Numeric values of these parameters at each visit and their corresponding changes from Baseline will be summarized by treatment group.

For each parameter, the frequency and percentage of subjects within each treatment group who have "Low," "Normal," or "High" Baseline values, then subsequently have "Low," "Normal," or "High" follow-up values at each assessment will be presented in a shift summary.

12.5.3 Pregnancy Test

Females of childbearing potential will undergo a urine pregnancy test at Screening followed by urine pregnancy tests at Baseline and every subsequent scheduled study visit. All pregnancy tests will be performed at study sites. Pregnancy status during the study will be listed.

12.6 OTHER SAFETY MEASURES

12.6.1 Electrocardiograms

All ECG assessments will be listed for all subjects. This listing will include the heart rate, the ECG interval from the beginning of QRS complex to end of the T wave (Q-T interval), the QT interval corrected for heart rate (QTc) (calculated using formulas by both Bazett and Fridericia as described in Section 8.4), the time between P wave and beginning of QRS complex in ECG (P-R interval), the electrocardiographic wave (QRS) duration, ECG results (Normal/Abnormal), whether there were clinically significant changes from Screening visit, whether abnormalities were present, and details and comments on any abnormalities. The ECG results at Baseline and changes at Week 16 will be descriptively summarized by treatment group. In addition, for QTc intervals calculated using both the Bazett and Fridericia methods, the number and percent of subjects with values ≥500 msec and the number and percent of subjects with changes from Screening of <30 msec, 30 to <60 msec, and ≥60 msec

will be presented. Additionally, each abnormality will be summarized by number and percentage of subjects reporting at each visit by treatment group.

12.6.2 Hospitalizations

Details for all hospitalizations will be listed. Number of hospitalizations for cardiopulmonary indications and total duration of hospitalization for cardiopulmonary indications will be summarized for each treatment group as well as overall number of hospitalizations and total duration regardless of indication.

12.6.3 Vital Signs

All vital sign assessments will be listed for all subjects. This listing will include height, weight, body mass index (BMI), heart rate, systolic and diastolic blood pressures, respiratory rate, and temperature. The vital sign results at each assessment and changes for each post-Baseline assessment will be descriptively summarized by treatment group.

12.6.4 Exacerbations of Underlying Lung Disease

Exacerbation of underlying lung disease is defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality. Number of subjects with exacerbation of underlying lung disease will be summarized for each treatment group and included in the overall AE summary table. A listing of these events will also be provided.

13 PHARMACOKINETICS

No pharmacokinetic measures will be assessed in this study.

14 REFERENCES

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15 LIST OF TABLES, LISTINGS, AND FIGURES

15.1 LIST OF TABLES

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14.3.4.7	Summary of Subjects with ≥20% Decrease in FEV1 from Baseline
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16.2.2	Protocol Deviations
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16.2.3.2	Analysis Population Information
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16.2.4.1	Demographics
16.2.4.2	PH-ILD History

Listing Number	Listing Title
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Summary of Changes

Statistical Analysis Plan - RIN-PH-201

Amendment 1 (Final SAP) - 12Dec2019

Original Statistical Analysis Plan (27 February 2019)

Amendment 1 (12 December 2019):

- The ordering of secondary and exploratory endpoints were re-ordered in the SAP Amendment 1 and differ from the order specified in RIN-PH-201 Protocol Amendment 3.
- In the protocol, time to clinical worsening was identified as an exploratory endpoint.
- In the SAP Amendment 1 analyses, time to clinical worsening will be analyzed as a secondary endpoint.

EXHIBIT 25

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUTREPIA™ safely and effectively. See full prescribing information for YUTREPIA™.

YUTREPIA™ (treprostinil) inhalation powder, for oral inhalation
Initial U.S. Approval: 2002

----------------------------INDICATIONS AND USAGE--------------------------

[redacted]

- [redacted]
- [redacted]

------------------------DOSAGE AND ADMINISTRATION---------------------

- [redacted]

---------------------DOSAGE FORMS AND STRENGTHS---------------------

[redacted]

-------------------------------CONTRAINDICATIONS------------------------------

[redacted]

------------------------WARNINGS AND PRECAUTIONS-----------------------

- [redacted]

-------------------------------ADVERSE REACTIONS------------------------------

[redacted]

[redacted]

[redacted]

Revised: 01/2024

[redacted]

[redacted]

[redacted]

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2 DOSAGE AND ADMINISTRATION

[redacted] [redacted]

[redacted]

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[redacted]

[redacted]

3 DOSAGE FORMS AND STRENGTHS

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

4 CONTRAINDICATIONS

[redacted]

5 WARNINGS AND PRECAUTIONS

[redacted] [redacted]

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5.4 Bronchospasm

[redacted]

6 ADVERSE REACTIONS

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- [redacted]
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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the [redacted]

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6.2 Adverse Reactions Identified in Post-Marketing Experience

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7 DRUG INTERACTIONS

[redacted]

8 USE IN SPECIFIC POPULATIONS

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10 OVERDOSAGE

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11 DESCRIPTION

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12 CLINICAL PHARMACOLOGY

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13 NONCLINICAL TOXICOLOGY

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14 CLINICAL STUDIES

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16 HOW SUPPLIED/STORAGE AND HANDLING

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17 PATIENT COUNSELING INFORMATION

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EXHIBIT 26

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EXHIBIT 27

REFINITIV STREETEVENTS

EDITED TRANSCRIPT

UTHR.OQ - United Therapeutics Corp at TD Cowen Health Care Conference

EVENT DATE/TIME: MARCH 05, 2024 / 5:50PM GMT

OVERVIEW:

Company Summary

MARCH 05, 2024 / 5:50PM, UTHR.OQ - United Therapeutics Corp at TD Cowen Health Care Conference

CORPORATE PARTICIPANTS

James C. Edgemond *United Therapeutics Corporation - CFO & Treasurer*

Michael I. Benkowitz *United Therapeutics Corporation - President & COO*

CONFERENCE CALL PARTICIPANTS

Joseph John-Charles Thome *TD Cowen, Research Division - MD & Senior Research Analyst*

PRESENTATION

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

44th Annual TD Cowen Healthcare Conference. I'm Joe Thome, I'm one of the senior biotech analyst here on the team at TD Cowen. And it's my pleasure to have with me today the team from United Therapeutics. We have President and COO, Mike Benkowitz and CFO and Treasurer, James Edgemond. Thank you both for joining us.

QUESTIONS AND ANSWERS

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

So maybe just to start things off, congrats on the record revenues in 2023. Maybe just give us a brief overview of the company's recent progress and your outline goals for the rest of this year?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Thanks, Joe, and thanks for hosting us today. Before I get started, my lawyers would want me to say something about forward-looking statements. So there you go. You guys can check out our public filings with the SEC to look at the risks and uncertainties associated with that.

So yes, 2023 was really a fantastic year for us, and I think it sets us up well for the future. What we're really focusing on, really last year, this year and in the future is executing on what we've called the 3 ways of growth that we've been talking about the last few investor conferences and at our last earnings call. So the first wave is what we call the foundational wave, which is really about commercial execution with respect to our already approved products, continuing on the recent growth trajectory from a revenue standpoint with those products.

The second wave is the innovation wave and really there, what we're focused on is development and then eventually commercialization of ralinepag in pulmonary arterial hypertension, PAH and then Tyvaso in IPF and PPF or progressive pulmonary fibrosis.

And then the third wave is what we call a revolutionary wave and that's our organ manufacturing business. And so we now have a really well-rounded multiple shots on goal approach to developing an unlimited supply of commercial organs in the kidney, heart, lung and liver space.

So that's really, I think, at a high level, what we're focused on, specifically with respect to 2024, it's really 4 things. One is to continue, like I said, continued revenue growth in the -- along the same trends that we saw in the last couple of years, 20% plus. We're looking on the innovation side, we're looking to complete enrollment in the ralinepag study and the 2 IPF studies with Tyvaso.

On the revolutionary side, where we expect to complete the preclinical work for the xenokidney and this quarter actually and then hopefully get a meeting with the FDA later this year that will lead to commencing a clinical trial as early as 2025. And then we're also excited with one of our recent acquisitions, Miromatrix, to begin the first human clinical trial with a bioengineered organ, which is the miroliverELAP.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

And the company has previously indicated, hoping to achieve a $4 billion run rate by the end of 2025. I guess what are sort of the key aspects of the commercial franchise that get you there? And maybe what proportion of that is going to come from? Tyvaso versus the rest of the franchise?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So we said $4 billion run rate by mid-decade. So 2025, 2026 in that time frame. And really, if you just kind of draw a line or extend the growth over the last couple of years, we're well positioned to do that. The lion's share of that growth will come from Tyvaso, particularly (inaudible) associated (inaudible) where we are currently the only approved therapy for that disease. Continue to make good traction in identifying those patients that are good candidates for that therapy.

But we also expect to, at a minimum, maintain Remodulin revenues. Though even with that said, last year, we actually had modest growth in Remodulin on our U.S. business, which is, we think, pretty phenomenal given that we've had a generic competitor for 5 years now. And then we expect to run (inaudible) to continue to grow on the heels of the expedite data, which we published a couple of years ago. And then we have a new study with Remodulin to Orenitram transitions, which is our ARTISAN study.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Okay. And obviously, the Tyvaso expansion into PH-ILD has been a huge investor focus and good for the top line. Can you tell us a little bit how many patients have you treated with PH-ILD or rather how penetrated into this market are you? Just kind of overall, where is the franchise there in terms of patient finding and how penetrated drug is?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So for PH-ILD, if you look at the epi data, it's a pretty broad range. I think the epi data suggests anywhere from 15% tied to 85% of the 230,000 ILD patients have or will get pulmonary hypertension. We've tended to really kind of focused on the low end of that range, 15%. So we look at the market as being around 30,000. I think you talked to various KOLs. I'd say it's significantly higher, but 30,000 is a good number for us to start with. It's almost as large as the PAH market. And as I said earlier, we're the only approved product in that space. So that's really kind of how we think about the size of the market right now.

And then in terms of penetration, we're in kind of the low double-digit range there, kind of in that 10% to 15% range and then continue to make progress every month, every quarter, every year and growing that patient base. And so we've undertaken, I think, several steps, which I'm sure I'm going to talk about, to continue to increase that penetration, educate those ILD physicians about pulmonary hypertension, steps they need to go through to screen those patients. And then at that point, they have a decision about whether they want to treat or refer to a PAH clinic.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

And maybe along that point, the company did expand the Tyvaso sales effort and sales force in 2023. Maybe if you can just remind us how large an expansion this was maybe what was driving this decision, if anything different than what you just highlighted? And maybe when will we start to see the impact from that expansion in revenues?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So I mean the expansion actually, I would say, the expansion of our field-based teams actually started about 12 to 15 months ago. So it was broader than just the sales representatives. We increased our medical science liaisons. We increased a team that we call our regional nurse specialists.

So these are nurses that we employ to go in and work with nurses in the office and teach them how to use our products, how to titrate, how to manage side effects.

And then we also deployed last year a team of what we call field reimbursement managers and the goal of that team or the objective of that team is, again, to go work with offices, particularly new prescribers and help them navigate the reimbursement process. We're filling out the referral form with how to write an appeals letter. So educating them on that whole process, because it's a pretty complex process for those practices that are used to dealing with our therapies.

And then the second half of last year, we augmented the sales team. So on a numbers basis, the sales team, we increased like say by maybe 25%. But really, I think the impact is going to be greater than that, because in addition to increasing the size of the teams, we also realign promotional priorities. So we now have a group of sales representatives that are only calling on ILD doctors and talking about PH-ILD. So the magnitude impact of that is greater than 25%, because they're now spending 100% of their time talking about PH-ILD.

And so really, what I think was just a recognition -- the reason we did it was just a recognition by us that we needed to provide more support, there was more opportunity out there that we maybe weren't optimizing. I think we felt like the -- maybe the sales representatives were spread a little (inaudible) of why they were reaching all the prescribers, the frequency by which they were able to talk to them and educate them wasn't where we thought it needed to be.

So that expansion on the sales force started middle of last year. You have to go through the hiring process, the training. So really, they deployed in earnest 1st of this year. And so it'll probably take a couple of quarters, really, I think, to start to see traction on the benefit of that. So as we get to the second half of the year, we would expect to see the payoff from that investment.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And the company does typically highlight seasonality in the fourth quarter and first quarter, at least relative to Q2, Q3. But obviously, in the last quarter, we did see quarter-over-quarter growth in Tyvaso specifically. Did this kind of buck the trend? Or is there underlying seasonality still in Tyvaso? Or what was sort of behind that growth?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So there's a natural seasonality to our business. We talked about this on prior calls. It's really a function of when we look -- at least when you look at the revenue line, because we have 2 specialty pharmacies, right? So it's a closed channel really 2 customers. They have an algorithm for which they can determine how much they're going to order, that's tied predominantly to shipping data in the quarter. So when you get into the fourth quarter, you really lose 2 to 3 weeks with the holidays in terms of shipping days. On the physician patient side, there's also fewer clinic days. So fewer days for physicians to see the patients.

And then we see this phenomenon often typically between Thanksgiving and Christmas where, just because of the complex nature of our therapies, patients will often wait until after the first of the year. So we may have referrals and prescriptions coming in. The starts may not occur until after the 1st of the year. And so that happens really across what we see that to varying degrees across all of our products. And so that -- we saw that in Q4 on a relative basis. But particularly with Tyvaso, we were able to grow through it, right, just because of the volume that was coming through.

Now the interesting thing is we didn't see it the prior year when you're looking at the revenue line, if you look at the underlying drug product going out to patients, we actually grew through it last year, too. The challenge we had last year, as you recall, is we had this inventory adjustment, because we were -- we had the nebulizer. We launched DPI. And so the specialty pharmacies were having to adjust their inventory levels to draw down their nebulizer inventory while they were stocking up on the DPI side. And so when you look at the revenues last year, it looks a little wacky. It looks like we actually had a down quarter, but the underlying metrics were still really strong. And so we saw that again this year as well.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And then maybe on the capacity with the DPI is all of that now behind us, nothing related to that? And then maybe if you can give a high-level update on the capacity expansion, just in preparation for IPF and PPF successful?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Yes. So the capacity issues that we were running into last year are behind us. MannKind, who's our partner and is manufacturing DPI for us, made some enhancements to their production lines, so they're able to increase production in the middle part of last year. And then as we move to the second half of the year, where we're seeing the benefit of that. We're bringing online actually this month, a kitting line down in North Carolina, so to keep this at a high-speed kitting line, because that has been sort of our last bottleneck to the extent there was one is that we were using a third party and they weren't moving as they were limited on how fast it could move. So now we've got a high-speed kitting line.

So those issues are behind us and the specialty pharmacies are able to order, rely on fleet within their contractual limits. We're starting to build up a little bit of inventory ourselves and that will just continue as we move into the balance of the year. Not to mention MannKind is adding 2 high-speed filling lines. And so that will increase our capacity when that comes online later this year, that will increase our capacity to support up to 25,000 patients a year.

And then as we think about IPF, just to kind of round that out, we have a new production facility that we broke ground on last year in North Carolina to further manufacture DPI and that will have a capacity for an additional 50,000 patients. And that should come online right around the time that we launch into IPF.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. Maybe on the Tyvaso DPI uptake in the field yesterday on our physician panel, the doctor indicated, there's actually still quite a bit of use of the nebulized product, especially during maybe dose titration and getting patients up to speed. Maybe overall, can you tell us where are people using the DPI? Are they converting their new patients? And are you seeing the same level of use of nebulizer to DPI? Or how is it fitting in?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So if you look at our revenues the last few quarters and the last couple of quarters, I guess, where we've broken out DPI and nebulizer, I think it's roughly a 60-40 split in terms of DPI. And that's tracking well when we look at the patient level data in terms of the mix of patients. I would say that new prescriptions coming in, new referrals coming in are more along the lines of 70-30. So over time, you would expect -- we would expect that the revenue is going to reflect that, and I think it will.

So in terms of where the DPI is coming from, initially, it was a lot of transitions of patients on nebulizer that wanted the benefit or the convenience of the DPI. That's largely played out at this point. So patients that were on the maintenance dose of neb and wondering to transition to DPI have transitioned over. And so DPI now is really -- I think it's really kind of starting to solidify itself as sort of frontline prostacyclin therapy in PAH and then obviously in PH-ILD which we've talked about.

So those are -- on the PHI there's going to be prostacyclin-naive patients. Could also -- we are also seeing some transitions from the orals. So selexipag, for instance, if patients aren't doing well. That might be the next stop, depending on where the patient is in their disease progression.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Okay. And then we do have an FDA decision coming up for Merck sotatercept later this month. Maybe if you could talk just a little bit about how you expect sotatercept to impact the PAH business, I guess just the landscape overall and then -- and as it relates to your top line as well or any of the product usage?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. I think over the, I mean, the medium to long term, we don't really see it impacting our business in a material way. And it's another therapy, they have very good clinical data. It's great for patients. I think as you look at -- you peel back the onion or the covers and look at their data and where it was used, how it was used. I think the things that we're really encouraged about is that 70% of the patients were on a background prostacyclin, like a Remodulin or Orenitram. So it does seem to suggest that those 2 products work well together.

So it's -- the other thing I would say is it's not a cure, it's not a replacement for prostacyclin. I think patients are still going to need prostacyclin. Increasingly, polytherapy is becoming the norm in PAH. And so you have the various pathways you cover with a PDE5 and the [RRA] prostacyclin, and this is the fourth pathway. So I think it's additive to the products that are out there. I don't really see it as being a replacement for any one product, including ours.

And I think the nice thing for the patients and us from a financial standpoint is if the drug is working really well, then sensibly the patients are going to live longer, they're going to stand our therapies longer. So that's kind of how we see it's another the tool of the toolkit for the physicians to use. But long term, we don't really see it impacting our business.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And obviously, there's some ongoing litigation with Liquidia. So we're not going to ask specifically about those decisions. But I guess how do you see Liquidia as a potential competitor? Is that factored into your business model at all? Or maybe why is the DPI, even if liquidity were to come to market saying PAH could be the preferred agent?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Did you say why would Liquidia become the -- I think I believe -- we believe Tyvaso will continue to be the preferred agent for very -- I mean the big one is that we've got 2 years of patient data, thousands of patients on the product. The patients are -- satisfaction level is incredibly high both by the physicians and by the patients. And so they have that experience with our product, which is incredibly helpful.

I think -- we think the convenience of our device as a differentiator. Ours is one (inaudible) per session. Their's 2. Ours doesn't require cleaning. Their's does. We don't have a max label dose. And so we just think, all in all, the patients and the physicians are going to prefer our product. We think the other thing that's attractive about our devices are just what's called a low-flow device and so that means that it requires less patient effort to actually breed the drug.

And then as a result of that, that property or that characteristic. The drug is actually getting deeper into the lungs. So what you see with a high flow device, which is what their device is. So we think all in all, the totality of the characteristics of our device are going to be preferred by physicians and patients.

And then on the payer side, you were in these discussions right now with payers and kind of working that out. But I think we're feeling increasingly confident that there's not going to be preference, so it's going to be a level playing field. So it's really going to be up to the patient and the physician, and we feel confident about how we're going to do there.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And then you mentioned earlier the Tyvaso in IPF and PPF yesterday on the panel, again, the physicians are really impressed with the increased data and sort of even in the placebo patients when you give Tyvaso, you do see that recovery in FVC. I guess what in the data package has resonated best with physicians? And maybe what -- can you update us on the status of the IPF and PPF program?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Well, I think the main thing is the FVC improvement that we saw in the increased data, the physicians have been really excited about it. This trial has been enrolling incredibly fast. We were able to actually increase the sample size last year without sacrificing any of our time lines. So I think both trials now are -- there's 2 trials. There's a U.S. trial. There's a rest of world trial, both our sides are around 575 patients. And we expect to complete enrollment this year in both trials. It's a 52-week study. So we'll get the last patient in end of -- towards the end of 2025 and then expect to have a readout soon thereafter.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And can you talk a little bit about the addressable patient population in IPF, PPF? I guess, where would the drug fit in into this treatment paradigm?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. So for IPF in the U.S. We see that as a patient population of about 100,000 patients. And in the TETON trials, patients can be on background therapy. So it will be additive to the existing therapies that are out there. In PPF, it's we think it's roughly 60,000 patients in the U.S.

So again, another unmet need that where patients can benefit from Tyvaso. And then in the case of IPF, I think we'll actually do this in PPF, but IPF for sure, we designed that to support our European filing. So we would expect to file in Europe and launch there soon after getting FDA approval.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. Maybe jumping over to the oral prostacyclin side of the business. I know we've discussed previously how some of the Orenitram data maybe hasn't or kind of was impacted by COVID in terms of relaying that to physicians, which maybe didn't get the full impact of that data set out to the market. I guess how is Orenitram launching now? How big do you think this could get? And then we'll dive into ralinepag after that.

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Yes. So I mean, it's interesting with Orenitram, because if you look at the clinical data for all of our products, it's far and away our best data. I mean you've got clinical works team, you've got improvement in some of the risk factors that physicians look at for patients in PAH. You've got an indication of survival at a cost that's actually less expensive than (inaudible).

So the whole package there is -- the value prop for Orenitram, we think is really high. I think the challenges that we see sometimes with Orenitram is its titration is good and bad, right? I mean it's good that you can titrate up. It's also a little bit more complicated to communicate to the patient. And then you have just the normal side effect things that happen with the prostacyclin. And so I think the words getting out on the data. I think what we have seen or what we found is that the -- I think the ideal place to use Orenitram is after Remodulin.

So that was the whole point behind the expedite study. So these aren't Remodulin patients that are sitting on Remodulin for years and transitioning over. Although we do have patients like that. But the idea with the expedite study was to take a patient that you would otherwise start on Orenitram, start them with Remodulin, get them up to a good dose over a period of weeks. Some doctors have done it in days, but really the study was to do it over a number of weeks, then be able to transition the patient over to a higher level dose of Orenitram with fewer side effects.

And so I think we're finding increasingly that the doctors are using that protocol to start patients on Orenitram. So that's really starting to get traction. And I think that's why we're seeing continued growth on Orenitram and that should continue.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

And then you have ralinepag in clinical development. I guess, how would this fit into the treatment paradigm as it is right now? Would this be sort of a direct swap for Orenitram? Obviously, we talked about dose titration just now and sort of some of the data you have in relation to Remodulin. But could all of that be essentially seen as also captured in ralinepag? Or do you see it in a different setting?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

I think it remains to be seen. I think we'll see what the trial bears out in terms of the efficacy titration, how high (inaudible) and patient outcomes. And I think we certainly see it as a direct competitor to selexipag is the same class of drug, IP receptor agonist. And so -- and with the once-daily dosing, we think that that's going to be an attractive option or alternative to selexipag. And then like I said, depending on the data, we'll see how that competes with Orenitram and there are properties of prostacyclin that patients benefit from over an IP receptor agonist. I think regardless of how this plays out, there's always going to be a role for Orenitram.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. Maybe on the xenotransplantation side, the company has indicated that they're now in pivotal preclinical studies for the xenotransplantation therapy. Maybe just at a high-level progress on that side of things? And what are sort of the pivotal preclinical studies that you need ahead of moving into the clinic?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Going to let my friend, James, answer a question.

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Yes. Thank you. So overall, we are continuing to make very good progress. And as lead Dr. Leigh Peterson said on the last earnings call, we are in discussions with the FDA in terms of satisfying their request for data in baboon studies. And so we're progressing those final studies this year, continuing conversations with the FDA with the goal next year, Joe, early of 2025 to get an IND approved for human clinical trials in xenotransplantation. So that's kind of the goal. And I think the progress has continued. And as an organization, we're very excited, and we're doing what the FDA has asked at this point.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And as it relates to the xenotransplantation side of the business. Can you remind us the current footprint that you do have in terms of facilities and maybe what spend was associated with the current (inaudible)?

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Sure. So what we announced a few weeks ago was we did a ribbon-cutting grand opening for a facility in Christiansberg, Virginia that we will use for growing the pigs that will be used for human clinical trials. And what we've said publicly is that facility was about $75 million that we established, we finished construction, and that will -- we're starting to get ready again to play into the time lines of working with the FDA to start human clinical trials in early or 2025. And that should be a good footprint for us to get to where we need. And then from there, we would expand into the commercial designated pathogen-free facilities.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

And that is one of the questions that we do get is how large of an expansion you would need to do for commercial opportunities. So what is the company thinking in regards to that? How many facilities would you need? And maybe what are the major derisking steps? Obviously, you mentioned the derisking steps to get to where you're at right now. But in order to turn on that additional investment, what would you want to see, I guess, in the clinic?

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Yes. Thank you. So we've talked publicly about in terms of these areas, we do want to initially start, and I'll talk about when. But with the commercial DPF facility and we've targeted a range for a cost to be between $1 billion and $2 billion. I think it will settle out somewhere in between and you can average use an average of $1.5 billion. What we are anticipating and planning to do is once we get an IND approved with the FDA, we will evaluate kind of the protocol there and start to understand how the clinical trial can roll out.

What we will do at that point because it's going to take about 3 years to build a commercial-scale designated pathogen-free facility, but we want to make sure we're doing it in a very thoughtful and methodical way. So that the human clinical trial moves forward, we're understanding that process and then starting to construct the facility. But we're going to do it in a way where we can watch the clinical trial and we can start to spend money because we won't downstroke a check in day 1 for $1.5 billion on average, but that will happen in time, and we want to be very thoughtful, methodical about how we spend the money and making sure that we understand the clinical trial and where it's going so that we can make sure at the end of that clinical trial, we're in a situation and a position to be able to supply transplantable organs to those in the.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. And on the last quarterly update, the company did announce that the FDA has cleared the IND for the miroliver ELAP program. Maybe just overall. Can you discuss the rationale for the Miromatrix acquisition? And what would an initial trial look like post this IND?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Yes. So the Miro we did -- we actually did 2 acquisitions last year, Miromatrix, and IVIVA. And really, the goal there, the objective there was really to kind of round out our organ programs. That gives us some more shots on goal. So we had been -- we had the xeno programs that we've talked about. We have a regenerated lung program, and then we have an autologous lung program on a 3D-printed scaffold that we've been working on. So this gives us another shot -- more shots on goal in the kidney and the liver. So that was really the rationale behind doing those.

In terms of the miroliver ELAP trial, I think the important thing there is that it serves the first bioengineer organ that's going into clinical trial. I think as a product, it's probably a niche product, but it kind of starts or continues our discussion with the FDA around what this clinical trial design look like and for all of our programs. So that's really, I think, the more important thing to think about with the ELAP.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. Obviously, touch on those 2 acquisitions, discussed about investment in the facilities for the xeno pipeline. Potentially, we'll have a lot of cash if you mean your goals over the next several years. I guess how does BD factor into that is BD a priority for the pipeline? And what would you be interested in?

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Yes. So thank you. So just to remind maybe the audience, we do have a capital allocation kind of waterfall. And in order the priorities for us continue to be research and development, which means we're investing in ourselves, both in clinical trials as well as facilities. And the second capital allocation

priority is business development. And there, we do dedicate time, dedicate resources to look at opportunities that we can bring into the organization to provide the highest and best use of capital. We try and be very thoughtful. And we look at organizations that are synergistic to the strengths of UT and the unitarians for manufacturing to sales, the clinical trials and even as Michael just discussed, show in manufactured organs.

So it is something that we continue to look at. We just want to be very thoughtful about bringing something in and making sure we have the right resources to advance that forward and the areas could be cardiovascular, again, things where we have strength and knowledge of rare lung disease. Again, as Michael talked about, getting into the organ manufacturing space to supplement and bring in new ideas and technologies that advance that overall program forward.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Perfect. Excellent. And with that, we are out of time. So thank you all for joining us.

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Thank you.

James C. Edgemond - *United Therapeutics Corporation - CFO & Treasurer*

Thank you.

EXHIBIT 28

REFINITIV STREETEVENTS

EDITED TRANSCRIPT

UTHR.OQ - Q1 2023 United Therapeutics Corp Earnings Call

EVENT DATE/TIME: MAY 03, 2023 / 1:00PM GMT

OVERVIEW:

UTHR reported 1Q23 revenues of $0.5b.

CORPORATE PARTICIPANTS

Dewey Steadman *United Therapeutics Corporation - Head of IR*

Leigh Peterson *United Therapeutics Corporation - SVP of Product Development*

Martine A. Rothblatt *United Therapeutics Corporation - Founder, Chairman & CEO*

Michael I. Benkowitz *United Therapeutics Corporation - President & COO*

CONFERENCE CALL PARTICIPANTS

Andreas Argyrides *Wedbush Securities Inc., Research Division - Analyst*

Ashwani Verma *UBS Investment Bank, Research Division - Director of Americas Equity Research & US Specialty Pharma Analyst*

Eun Kyung Yang *Jefferies LLC, Research Division - MD & Senior Equity Research Analyst*

Hartaj Singh *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Jessica Macomber Fye *JPMorgan Chase & Co, Research Division - Analyst*

Joseph John-Charles Thome *TD Cowen, Research Division - MD & Senior Research Analyst*

PRESENTATION

Operator

Good morning, and welcome to the United Therapeutics Corporation First Quarter 2023 Earnings Webcast. My name is Danielle, and I will be your conference operator today. (Operator Instructions)

Please note this call is being recorded. I would now like to turn the webcast over to Dewey Steadman, Head of Investor Relations at United Therapeutics.

Dewey Steadman - *United Therapeutics Corporation - Head of IR*

Thank you, Danielle, and good morning. It's my pleasure to welcome you to the United Therapeutics Corporation First Quarter 2023 Earnings Webcast. Accompanying me on today's call are Dr. Martine Rothblatt, our Chairperson and Chief Executive Officer; Michael Benkowitz, our President and Chief Operating Officer; James Edgemond, our Chief Financial Officer and Treasurer; and then Pat Poisson, our Executive Vice President of Technical Operations; and finally, Dr. Leigh Peterson, our Senior Vice President of Product Development.

Remarks today will include forward-looking statements representing our expectations or beliefs regarding future events. These statements involve risks and uncertainties that may cause actual results to differ materially. Our latest SEC filings, including Forms 10-K and 10-Q, contain additional information on these risks and uncertainties, and we assume no obligation to update these forward-looking statements.

Today's remarks also may discuss the progress and results of clinical trials or other developments with respect to our products. These remarks are intended solely to educate investors and are not intended to serve as the basis for medical decision-making or to suggest that any products are safe and effective for any unapproved or investigational uses. Full prescribing information for these products are available on the products' websites.

Now I will turn the webcast over to Dr. Rothblatt for an overview of our first quarter 2023 financial results and the business activities of United Therapeutics. Martine?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you, Dewey. Very excited to welcome everyone to another great quarter at United Therapeutics. We are thrilled to continue on course toward our mid-decade goals of 25,000 patients being treated for pulmonary hypertension and the doubling of our revenue run rate. This quarter, we moved toward those goals with double-digit revenue growth from first quarter '22 to first quarter '23. And that also includes, by the way, nearly 40% growth in our main growth driver, which is Tyvaso.

I think our double-digit growth rate remains a solid forecast even with the possibility of new FDA approvals of sotatercept or Liquidia. The reason is that sotatercept has not even been tested in our main growth market of Group 3 pulmonary hypertension. Indeed, systemic drugs are generally contraindicated there due to them causing V/Q or ventilation-perfusion mismatch. In the disease sotatercept was tested in, Group 1 pulmonary arterial hypertension, we expect it to be complementary to either our Orenitram, Tyvaso or Remodulin products. So we don't forecast a realistic threat from sotatercept to our growth.

(inaudible) Liquidia, if approved, also does not challenge our projected double-digit growth. It's because it's not a generic product, but is instead a strongly differentiated drug device product requiring 65% more drug to even match Tyvaso's effect based on their own clinical trial data.

Also exciting to report this quarter is the robust progress in our pipeline. We are spot-on target to fully enroll our current big Phase III trials by the end of next year, each of which have their own billion-dollar potential. In other words, the pipeline [shown] embeds more than double our current total revenues, and then there is the aforementioned organic doubling of our revenues from our existing products already commercialized and now entering the market, such as Tyvaso DPI, Remunity and our new Orenitram dose titration kits.

I'm also very excited to report big news on the use of capital front. We have allocated $0.5 billion to a new Tyvaso DPI manufacturing facility in Research Triangle Park, North Carolina, with 50,000 patient capacity. And by the way, this is in addition to our existing nearly $100 million allocation of capital to our new clinical xenotransplantation facility in Virginia.

By the way, speaking about transplant, I'd like to thank the dozens of our shareholders and other stakeholders who sent me Amy Silverstein's superb story of her heroism in the face of heart transplants and immunosuppressants. In that vein, I wanted to take a moment to update everyone on what we at United Therapeutics are doing to effectuate Amy's quest.

In our own lab center company, we reprogrammed differentiated cells from patients back to stem cells called iPSCs, or inducible pluripotent stem cells. By the end of this year, we'll be creating iPSCs from 2 patient donors every single month. In our own labs, we differentiate cells into different types of cells needed for cellularizing different organs, such as lung, including stromal cells and epithelial cells and different types of alveolar cells.

In our own labs, we grow differentiated cells in 3D chambers into the billions of cells needed to cover each organ. Indeed, in our own labs over the past 3 years, we have produced about 2 trillion cells every year.

Also in our own labs, we cellularize our organ scaffolds with the cells that we have expanded. Indeed, last month, we achieved a kind of (inaudible) level of proof of concept for one of our own cellularized lungs, provided a pig model with the level of (inaudible) considered acceptable for human lung transplants.

Again, in our own labs, we produce this time under GMP conditions about 500 lung scaffolds every year and are now working on 3D printing kidney and liver scaffolds in partnership with 3D Systems. In short, Amy's vision of an immunosuppressant-free organ transplant is realistic for this decade, the 2020s.

Here at United Therapeutics, we expect to have patient-derived, stem cell-differentiated autologous lungs, kidneys and livers in the clinic within 5 years. Hearts could also be done. No immunosuppressants would be needed because the transplanted organs will have the same DNA as the patient. So it is really the best of times here at United Therapeutics with record revenues, another $0.5 billion quarter, record pipeline potential, $2 billion-plus opportunities and record deployment of capital and business expansion.

At UT, our mantra is go big or go home. We are going big on pulmonary hypertension. We are going big on pulmonary fibrosis. And we are going big on creating an unlimited supply of transplantable, tolerable organs. Mike Benkowitz, our President and Chief Operating Officer, will now give you a deeper dive into the business. Mike?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Thanks, Martine, and good morning, everyone. We're pleased to report yet another quarter of meaningful growth for our treprostinil business. And as Martine said, we're really excited to have quarterly revenues of more than $500 million for the second time in our company's history.

As usual, I'm going to provide some color around what we're seeing with respect to each of our treprostinil products: Tyvaso, Remodulin and Orenitram. For Tyvaso and Tyvaso DPI, underlying physician and patient demand for Tyvaso remained exceptionally strong in the first quarter as we continue to grow our Tyvaso active patients at a clip consistent with the patient growth trends for the prior 3 quarters.

We saw a record number of referrals, which is what we call prescriptions, and new patient starts during the first quarter. We also continued to increase the breadth and depth of the Tyvaso prescriber base. Since the PH-ILD launch in 2021, we have now doubled the number of Tyvaso prescribers. That's our breadth metric. And in terms of prescribing depth, I've mentioned on prior calls that our key metric here is the number of prescribers with 3 or more Tyvaso patients.

I'm really happy to report that we've also doubled the number of prescribers in this category. The 3-plus Tyvaso prescribers now represent about 40% of all prescribers, which means we still have an opportunity to expand depth, which should pave the way to further accelerate Tyvaso growth over time.

The first quarter performance for Tyvaso saw the usual early year seasonality with respect to patient discontinuations due to insurance changes and also as usual, discontinuations returned to normal levels in February, March and in April. Importantly, discontinuations for Tyvaso DPI continue to run well below that of nebulized Tyvaso, reflecting patient satisfaction with Tyvaso DPI. So overall, we believe the underlying strength of the Tyvaso business is great.

Looking at first quarter revenue, as I said in the past, due to the nature of our business, we regularly encourage investors to look at longer-term revenue trends compared to quarterly revenue fluctuations. With that said, there were 3 main factors that impacted Tyvaso revenue in the first quarter, given that we're essentially in the middle of 2 product launches within the Tyvaso franchise, PH-ILD and then Tyvaso DPI.

First, and as we discussed last quarter, our specialty pharmacies are still rightsizing orders for the correct DPI and nebulized mix. In the third quarter of last year, specialty pharmacies made significant orders of nebulized Tyvaso in anticipation of increased PH-ILD demand without fully appreciating the potential for Tyvaso DPI demand.

Moving to the fourth quarter of last year and the first quarter of this year, we saw unexpectedly strong demand for Tyvaso DPI relative to nebulized Tyvaso. And the specialty pharmacies needed to reduce its nebulized inventory, which reduced Tyvaso revenue well under patient -- well under actual patient demand in the fourth quarter of 2022 and the first quarter of this year.

Second, we're seeing a higher level of PAP utilization for Tyvaso DPI than we expected. We believe this is a short-term phenomenon and will subside to a large degree when the Medicare changes that are part of the Inflation Reduction Act go into effect starting next year.

Finally, due to the incredible demand for DPI and the fact that we launched immediately upon approval without building inventory, we have not been able to allow specialty pharmacies up to their contractual minimum inventories each month. Based on our DPI demand trends and forecast, this is something that could persist for the balance of the year. Having said that, we are taking steps to increase DPI production capacity in both the short and medium term.

First, our partner, MannKind, is activating a second production line and additional kitting capacity from which we expect to see increased DPI supply as soon as this quarter. Second, and in parallel, MannKind is also on track to significantly expand manufacturing capacity in the first half of

next year to support up to 25,000 Tyvaso DPI patients a year. And finally, as Martine mentioned, we have initiated a construction project to build a new UT-owned and operated Tyvaso DPI manufacturing facility. That facility is intended to provide enough capacity to support an additional 50,000 DPI patients per year and with expansion capacity for up to 75,000 DPI patients.

Turning to Remodulin. This business continues to be incredibly resilient, even though it's faced a generic competitor for almost 4 years now. We saw the second highest number of referrals for Remodulin in the first quarter. And after a small dip in active patients following the generic launch of a subcutaneous version of Remodulin, our active patients are back to pre-generic levels. Remunity continues to gain traction in the market as it is the only subcutaneous pump widely available for new Remodulin patient starts, with Remunity representing over half of our monthly subcu Remodulin shipments during the quarter.

Finally, Orenitram had a very solid quarter, achieving record number of patients on therapy and record revenues. We launched a 90-day titration kit during the first quarter, which simplifies dosing and titration for new patients. While still early, physician and patient feedback has been very positive around the convenience of these new kits. There continues to be a lot of buzz in the physician community around the EXPEDITE data we top-lined last October, demonstrating that prostacyclin induction with Remodulin can lead to double the average Orenitram dose when patients shift to oral therapy and in a shorter period of time as compared to patients who do not have a Remodulin induction. We expect to publish a peer-reviewed manuscript detailing the study in the coming months.

To wrap up, we're very pleased with the overall treprostinil business, led by the incredible demand for Tyvaso DPI, and we believe we're on our way to hitting our goal of a $4 billion revenue run rate. With that, I'll turn the call back over to Martine to start the Q&A session.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thank you so much, Mike. Those were terrific insights into every one of the products. Really appreciate that color that you shared with everyone. Operator, could you please open the phones, and I will sort the questions to the person most appropriate for answering them.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) The first question comes from Joseph Thome of TD Cowen.

Joseph John-Charles Thome - *TD Cowen, Research Division - MD & Senior Research Analyst*

Mike, I know you mentioned that the Tyvaso DPI discontinuations are a little bit lower than what you were seeing with the nebulized Tyvaso. Maybe what are the expectations for the Tyvaso DPI average time on therapy versus what you were seeing with the nebulizer? And as we see sotatercept potentially launching maybe next year, do you expect the Tyvaso time on therapy could actually increase as these patients kind of continue to do maybe better than they did without sotatercept? Or would they intend -- maybe ramp down their prostacyclin use? How do you expect that to kind of play out?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Mike, looks like Joe directs his question to you.

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Thanks, Joe. So I think overall, we're really encouraged by the lower level of discontinuation rates with Tyvaso DPI. And we do think that, that augurs well for increased time on therapy. To put a number on that, I think it's still a little early to kind of say definitively what that's going to be. But certainly, patient satisfaction has been really high with Tyvaso DPI. I think it's led to better adherence, better compliance and that leads to patients doing better, and then that will ultimately lead to patients staying on therapy longer. So I think your premise, your hypothesis that time on therapy will increase with DPI over time is absolutely right. And that's something we're certainly expecting.

Similarly, I think sotatercept probably helps in that regard as well. If you look at the underlying data in the sotatercept study, 70% of the patients in that study were on a background prostacyclin. So as Martine said in her opening comments, we think there's a lot of complementary effects between prostacyclin and sotatercept. And so we would expect that when sotatercept is launched into the market, that will continue and patients will experience a nice benefit between the 2 products as well as the other products on background therapy and should continue to lead to increased time on therapy.

Operator

Next question comes from Hartaj Singh of Oppenheimer.

Hartaj Singh - *Oppenheimer & Co. Inc., Research Division - Research Analyst*

Nice update, everybody. Just had a question on Orenitram and the EXPEDITE study. I know at ERS last year in Barcelona, really big updates there and educating the patient-physician community. It seems like at ATS this year, again, you will kind of delve into that. If you can just talk to us a little bit about what the patient flow is. Are patients mostly starting on Remodulin and then going over to Orenitram? Or are they still starting on Orenitram -- or what's the breakdown? And then how can we expect sort of that to benefit Orenitram going forward? I know it already is, but could that add even more going forward?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Great question, Hartaj. Mike, I think you'd, again, be the best person to address that question.

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. Thanks, Hartaj, for the question. So in terms of kind of the mix of patients between starting de novo on Orenitram and transitioning from Remodulin, I think it's roughly, call it -- 2/3 roughly, 2/3 of patients are starting de novo on Orenitram right now. And as I mentioned in my comments, I think the fact that we've got that titration -- new titration kit, I think that's going to continue to help patients titrate up on Orenitram, starting de novo, and then the balance are transitions from Remodulin.

I still believe that there will be patients that will start de novo on Orenitram over time once we really fully, I think, take advantage of the EXPEDITE data. But I also think it's true that Tyvaso DPI is proving to be so convenient for patients, and it's almost sort of your gateway drug to prostacyclin. So I think over time, you're going to see a higher number -- higher percentage of patients initiate prostacyclin therapy on DPI, even over the orals, both Orenitram and selexipag.

And so the thing that we really like about the EXPEDITE data and then the ARTISAN study, which we've talked about on prior calls, is it's an opportunity to take these maybe functional class III patients or even IV patients in the case of ARTISAN, start them on Remodulin, get their hemodynamics down -- closer to normal levels. And then you can flip them over to Orenitram and really use Orenitram as their maintenance drug and continue to titrate up as you need. And if they -- if over time, they decline, then you can obviously switch them back to Remodulin.

But we really see that as sort of a key position for Orenitram as we move forward over the next several years. And in some, it really just kind of speaks to the flexibility of treprostinil and the fact that we've got these different delivery options. And so it really just, I think, allows us to kind of meet the patient -- the physician where the patient is in their disease progression.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Great. Thanks so much, Mike. That was really beautiful, the way you were able to describe that with ARTISAN and EXPEDITE and the whole rapid transition to oral. We're able to get patients into a stable equilibria, if you will, with their pulmonary artery pressures down around, I would say, below 40 millimeters of mercury. And there's like an increasing volume of data out there, well over a dozen scientific papers that have shown that patients with pulmonary hypertension who are managed in this kind of potential, well between 30 and 40 millimeters of mercury, are able to achieve very long-term survival, 10, 20 years out to the limit of the papers -- of the data that the papers had access to. And those are papers by independent physicians, not from us.

So we really believe that our initial mission of the company of being able to keep patients with pulmonary hypertension living with pulmonary hypertension instead of dying from pulmonary hypertension has been very largely achieved with the combination of parenteral prostacyclin to rapidly get their pressures down and then oral prostacyclin, Orenitram, to be able to keep them stable in the long term.

Operator

The next question comes from Jessica Fye of JPMorgan.

Jessica Macomber Fye - *JPMorgan Chase & Co, Research Division - Analyst*

On the plans to increase capacity for Tyvaso DPI, that sounds pretty bullish with respect to the anticipated demand trends there. And it sounds like you're seeing nice net patient adds as well. But can you just confirm whether there's any capacity constraint on DPI right now that's at all limiting to patient adds? Or is it that you're keeping up with patient demand and then in the near term, the capacity is maybe just keeping the specialty pharmacies from reaching target inventory levels?

And just related to that, I think you said Tyvaso net patient adds were in line with the past 3 quarters. Can you just remind me what that run rate was that you're tracking in line with?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Okay. Thanks so much for the questions, Jess. There were several questions there. So let me start with the production expansion questions. And then, Mike, if you could queue up your responses to the rest of the questions that Jess asked there.

So Jess -- so we are pretty bullish on our forecast for Tyvaso DPI. And the maximum capacity of the MannKind facility up in Danbury, Connecticut will be -- by the beginning of next year will be for 25,000 DPI patients. So we'll be entering '24 with a capacity for 25,000 patients.

Now as I mentioned in my introductory remarks, our company's goals for the middle of the decade are being able to treat 25,000 pulmonary hypertension patients. So if a large proportion of those 25,000 patients are on Tyvaso DPI, which is, I think, reasonable, then it would be like, well, where is the production capacity for the go big on pulmonary fibrosis? Where is the production capacity for what we think the pulmonary fibrosis market will be?

Well, best as we can tell, we expect the pulmonary fibrosis market to actually be for Tyvaso DPI even larger than the pulmonary hypertension market. So we would need more than an additional 25,000 patient capacity for the pulmonary fibrosis market. And indeed, the market research and the disease-modifying hypotheses that we have for Tyvaso DPI in pulmonary fibrosis is such that we could easily expect to have 50,000

pulmonary fibrosis patients being treated in addition to the 25,000 mid-decade pulmonary hypertension patients. So that's the reason why we need to start now deploying a substantial amount of capital to build this brand-new Tyvaso DPI production facility in Research Triangle Park, North Carolina.

As Mike mentioned, even that facility, even though its launch capacity will be 50,000 patients, it will have a surge capacity to go up to 75,000 patients. So we think between the 25,000 at MannKind, the 50,000 in North Carolina, the surge to 75,000 in North Carolina, as we enter the 2026 time frame, we then have a capacity to support 75,000 to 100,000 DPI patients, which would cover our needs for both Group 1 pulmonary hypertension, Group 3 pulmonary hypertension, idiopathic pulmonary fibrosis and additional forms of pulmonary fibrosis that go under the rubric of proliferative -- progressive pulmonary fibrosis, which in fact, we are embarking on the other additional Phase III trial for.

So Mike, with those comments in terms of the production capacity, can you answer the other questions that Jess had?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Absolutely. So Jess, I think your question around your first -- first part of your question was around sort of patient demand versus SP demand to build up their inventory. So we're definitely in the category of the latter. So we're not having to halt or delay patient starts on DPI. We're making enough to meet the patient demand.

I think the issue that I was referencing in my opening comments is typically, specialty pharmacy, they have an algorithm for figuring out how much -- how they order every month. They typically try to order up to have, call it, roughly 2 months of inventory on hand and then over the course of the month, they'll get down to about 30 days. So they generally like to keep at least -- always be in a position where they have at a minimum 30 days of inventory on hand. So due to the demand, we're not able to kind of meet that need on the part of specialty pharmacy.

Like I said, we have some additional production capacity coming online as soon as this quarter. That will start to open things up a little bit. But I think really, as we're continuing to grow over the balance of the year, we're probably going to be in this situation where they're not going to be able to order up to the levels they're accustomed to ordering up to until, as Martine said, we get the significant expansion next year to get up to 25,000 patients.

Second part of your question was just sort of the average, I guess, the run rate in terms of patient adds. So if you look back over the last -- this quarter or the prior 3 quarters, it's kind of averaged out to around 500 patient adds per quarter on Tyvaso, and that's between both DPI and nebulized.

Operator

The next question comes from Eun Yang from Jefferies.

Eun Kyung Yang - *Jefferies LLC, Research Division - MD & Senior Equity Research Analyst*

I have a question on TETON trial. So we are expecting data in 2025. So based on the Phase III INCREASE trial, subgroup of patients with underlying IPF, we saw benefits on FVC up to 16 weeks. So TETON trial is a 52-week time point. So do you expect benefits on FVC to continue to increase to 52 weeks? And then can you comment on powering assumptions for the TETON trial?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thanks. Nice to hear your questions. I think it will be best to have Dr. Peterson -- she is in charge of running the TETON trial, answer your questions.

Leigh Peterson - *United Therapeutics Corporation - SVP of Product Development*

Yes. Thank you for your question. Yes, so in fact, the INCREASE study, indeed, the main study, the placebo-controlled study, was 16 weeks, as you mentioned. However, we do have an open-label extension study of the INCREASE data where we've looked to see how the patients do over the longer period of time, including the 52-week time period. And we still see benefits of patients on Tyvaso in the INCREASE population. So we feel confident that, that will translate to the longer period in the TETON studies.

And as far as the TETON study, they are definitely powered, I mean, we have 90% power to detect the difference that we've seen in the INCREASE studies with regard to absolute FVC. So we have sufficient power to see the difference over the 52-week period. So again, we feel confident on that.

Operator

The next question comes from Andreas Argyrides of Wedbush Securities.

Andreas Argyrides - *Wedbush Securities Inc., Research Division - Analyst*

Congrats on the quarter. When thinking -- so quickly, first, what's the status of the organ manufacturing programs? And when can we expect [first] program to enter clinical trial? And then how should we think about spend when it comes to organ manufacturing? And I have one follow-up.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Okay. We won't be able to take your follow-up, and Andreas, thanks for the congrats on the quarter. Your line broke up a little bit, but I think the gist of the question was to get an overview of the organ manufacturing situation and when we expect results of the organ manufacturing to enter into clinical trials. And I think you asked something about the capital associated with other spending.

So the organ manufacturing program is a broad, multifaceted, multiple shots on goal program. So it won't be really realistic to give an overview of everything beyond the really exciting things I mentioned this morning, in response to Amy Silverstein's passionate arguments, that part of our organ manufacturing program is strongly focused on organs that would not require immunosuppressants. In other words, autologous organs that are manufactured with the cells downstream from a patient's own donated cells.

And within different laboratories at United Therapeutics, we currently produce iPSC cells. In other words, we reprogram PBMCs and another differentiated cells from patients back into stem cells. We then used techniques proprietary to the company to then differentiate those stem cells into the different types of cells that we would cellularize organs with.

Other programs at other laboratories within United Therapeutics are based on allogeneic cell lines that we are able to MHC segment. So patients could expect a much lighter immunosuppressant load than if they were just taking kind of an average donor organ.

And then let me get to your question about the clinical trial. So the organs we have closest to clinical trials are our xenohearts and xeno-kidneys. These are hearts and kidneys from donor animals that have been grown under the equivalent of good manufacturing practices conditions, what are called pathogen-free conditions. And they have 10 genetic modifications that we believe will allow them to surmount hyperacute and acute rejection with no more than the normal commercially available immunosuppressants today and be able to continue on to a long-term duration in the recipient's body with the management of chronic rejection as is done today with allografts.

So those organs are currently in what's called by the FDA a pivotal preclinical program. That means it's the last preclinical program before going into a human study. And that program is -- hopefully, we will be able to complete that program by the end of '24 and be able to then enter into the first clinical trials in '25. So that would be kind of a bottom line answer to your question, that the first manufactured kidneys and hearts, hopefully, knock on wood, should be able to enter into clinical trials in '25.

Operator

The next question comes from Ash Verma of UBS.

Ashwani Verma - *UBS Investment Bank, Research Division - Director of Americas Equity Research & US Specialty Pharma Analyst*

I had one on sotatercept impact. So the feedback that we've heard from physicians indicates that Merck's product positioning and payer reception can have an important bearing on what part of your portfolio may get impacted. In your view, does that matter? And like what is the assumption that you have on competitors' pricing in line of therapy positioning?

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Okay. Thanks for the questions, Ash.

(technical difficulty)

like a frontline question, then Mike -- I mean, answer, then Mike will give you more of a definitive answer. But as I noted in our introductory remarks, we don't see sotatercept having any effect whatsoever on the growth guidance that we've provided for our company. And the reason for that is a lot of people are not completely clear that there are 2 different diseases that are treated with drugs such as ours that sound very similar and it's easy to get them confused.

So the disease that sotatercept was tested in and the disease that all of our drugs are approved for, all of our non-cancer drugs are approved for is called Group 1 pulmonary arterial hypertension, and the acronym is PAH. A different disease is called Group 3 pulmonary hypertension or just Group 3 PH. Sotatercept has never been tested, at least anything published that we're aware of, in Group 3 pulmonary hypertension. The only drug approved for Group 3 pulmonary hypertension is Tyvaso, including Tyvaso DPI.

And as Mike described very well, most of our growth in the coming years, we expect to come from Group 3 pulmonary hypertension. So by definition, sotatercept cannot have any effect on that growth trajectory whatsoever.

In addition to that, within the Group 1 pulmonary arterial hypertension, where we do continue to have growth across our franchise, I think Mike mentioned we had our highest quarterly sales of Orenitram ever, we expect sotatercept to be complementary. And Mike, would you like to expand on that?

Michael I. Benkowitz - *United Therapeutics Corporation - President & COO*

Sure. I'll just kind of pick up right there, which is, I think I said in response to an earlier question around this, we definitely look at sotatercept as complementary to our drug and the other drugs that are currently on the market to treat Group 1 PAH. It's another pathway. So now we have a drug to treat 4 different pathways associated with pulmonary arterial hypertension. If you look at the -- as I said, if you look at the data in the sotatercept trial, 70, 7-0, 70% of those patients were on prostacyclin therapy. So clearly, there appears to be a complementary or synergistic effects between prostacyclin and sotatercept.

So we think that all of the drugs will continue to be used. I think some physicians that we've talked to have talked about this sort of four corners approach of treating PAH, so you have a drug to treat each of the 4 pathways. How that gets sequenced and -- in the grand scheme of things, doesn't really matter because I think it's still a progressive disease. There was nothing in the sotatercept data really that suggest that it's a cure or even a disease-modifying agent. I know there were some speculation that, that might be the case, but I don't think that's borne out in the data.

So clearly, patients are benefiting from it, but I think it's a combination with the other drugs. And so we think over time, it's another drug that physicians can add to their treatment armamentarium, but it doesn't appear to be something that's going to replace or displace our products.

Martine A. Rothblatt - *United Therapeutics Corporation - Founder, Chairman & CEO*

Thanks so much, Mike. And thank you, operator, and everybody, for joining our first quarter conference call. Great work, Dewey Steadman. We'll be presenting at various and sundry health care conferences during the balance of the year, and we look forward to seeing you there and providing additional insights and color on United Therapeutics' business. Operator, you can disconnect the call.

Operator

Thank you for participating in today's United Therapeutics Corporation earnings webcast. A rebroadcast of this webcast will be available for replay for 1 week by visiting the Events & Presentations section of the United Therapeutics Investor Relations website at ir.unither.com.

EXHIBIT 29

TYVASO DPI®
(treprostinil) INHALATION POWDER

Instructions for Use

TYVASO [tī-vā′-sō] DPI®
(treprostinil) Inhalation Powder
For oral inhalation only

30131100602

Table of Contents

Read Before Starting

This Instructions for Use contains information on how to inhale TYVASO DPI (treprostinil) Inhalation Powder. Read this Instructions for Use carefully before you start using your inhaler and each time you get a new inhaler. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you how to use your inhaler the right way before you use it for the first time.

Parts of the TYVASO DPI Inhaler (see **Figure A**)

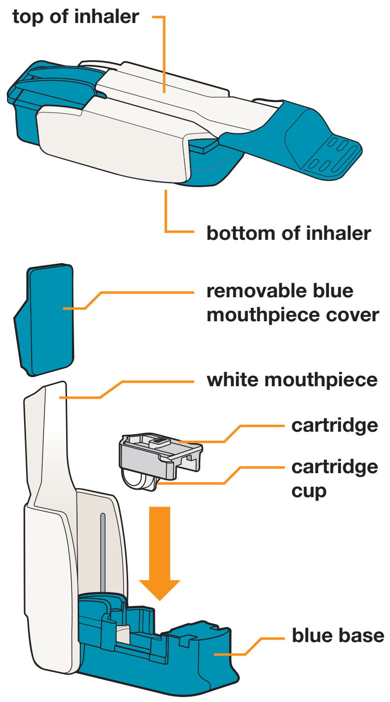


Figure A

Your Starter Kit includes a Carrying Case (see **Figure B**)

The TYVASO DPI inhaler and blister strips can be stored in the carrying case when using outside of your home or traveling.

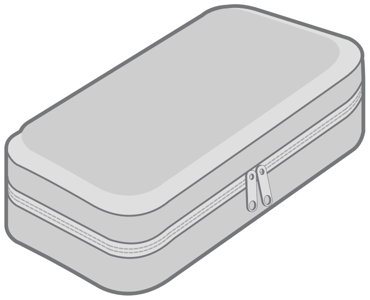


Figure B

TYVASO DPI Blister Cards (see **Figure C**)

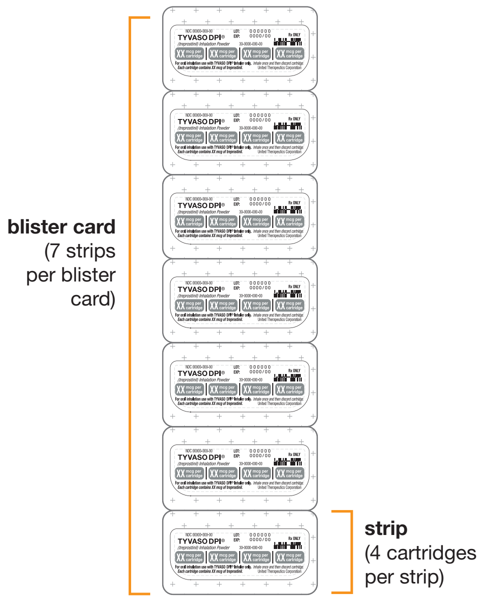


Figure C

Important Information

Important information you need to know before inhaling TYVASO DPI Inhalation Powder using the TYVASO DPI Inhaler

TYVASO DPI cartridges come in 4 strengths (see **Figure D**).
Important: Always make sure you have the right number of TYVASO DPI cartridges for your dose before you start. Only use TYVASO DPI cartridges with the TYVASO DPI Inhaler.

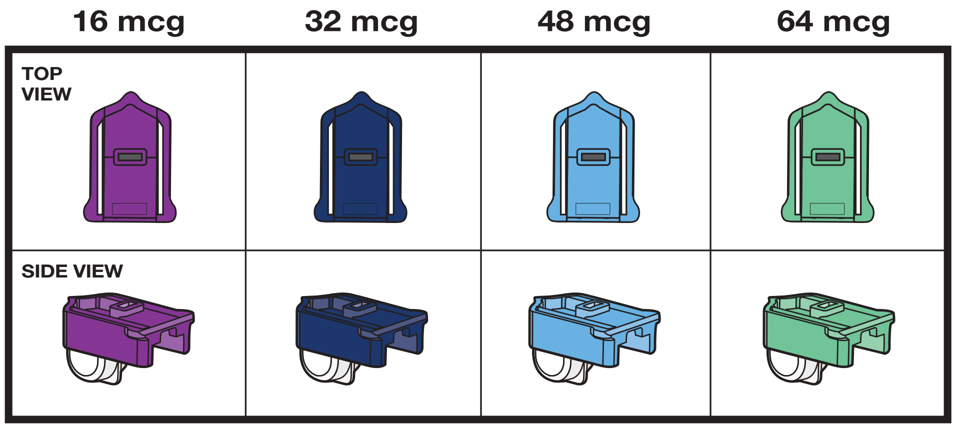


Figure D

If you are having problems with your TYVASO DPI Inhaler, have any side effects, or if your TYVASO DPI Inhaler breaks and you need a new one, please call 1-877-UNITHER (1-877-864-8437).

- Take TYVASO DPI exactly as prescribed by your healthcare provider.
- Take TYVASO DPI 4 times per day while you are awake, about 4 hours apart.
- If you miss a dose, take it as soon as possible at your usual dose.
- If your prescribed dose is higher than 64 mcg per treatment session, you will need to use more than 1 cartridge. If using more than 1 cartridge, the cartridges can be used in any order, regardless of cartridge strength.
- If you need to use more than 1 cartridge for your dose, remove the used cartridge from the inhaler before getting a new one. You can tell a cartridge has been used when the cartridge cup has moved from the front to the middle position in the cartridge base.
- **Only TYVASO DPI cartridges should be used with the TYVASO DPI Inhaler.**
- **Each cartridge is for 1 time (single use) only.** Use a new cartridge for each treatment session. After each treatment session, throw away the used cartridge right away.
- **Do not** open the cartridges. The inhaler opens the cartridge automatically during use.
- **Warning:** If any powder from the cartridge spills on your hands, throw away the cartridge right away into regular household trash and wash your hands. Then start with a new cartridge.
- **Do not** breathe in the TYVASO DPI treprostinil powder in any other way.
- **Do not** put cartridges in your mouth.
- **Do not** swallow cartridges.
- Use only 1 inhaler at a time. The same inhaler should be used even when needing to use more than 1 cartridge for your dose. Inhale 1 cartridge at a time.
- The inhaler lasts for 7 days. After 7 days of use, throw away your used inhaler and get a new one.
- Store the inhaler in a clean, dry place with the mouthpiece cover on until your next dose.

Storing TYVASO DPI Inhalers and Cartridges

Storing TYVASO DPI Inhalers

Store TYVASO DPI Inhalers, with the mouthpiece on, in a clean, dry place at room temperature between 68°F to 77°F (20°C to 25°C), such as a drawer or medicine cabinet (see **Figure E**).

Inhalers may be stored in the refrigerator between 36°F to 46°F (2°C to 8°C), but should be left out at room temperature for 10 minutes before use.

> **Do not** leave or store cartridges in the inhaler.
>
> **Keep out of the reach of children.**

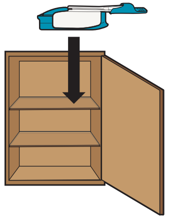


Figure E

Storing Unopened Blister Cards and Strips

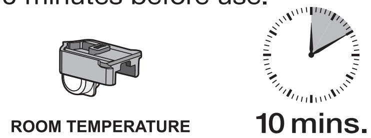
Store unopened blister cards and strips in a clean, dry place at room temperature, such as a drawer or medicine cabinet. You can store in the carrying case when using outside your home or traveling (see **Figure F**).

> **Do not** use after 8 weeks if stored at room temperature.

Unopened blister cards and strips may also be stored in the refrigerator (see **Figure G**).

> **Do not** use after the Expiration Date has passed.

Important: If refrigerated, cartridges and inhaler should be left out at room temperature for 10 minutes before use.



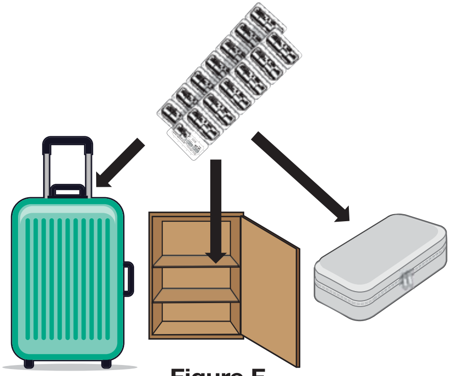


Figure F

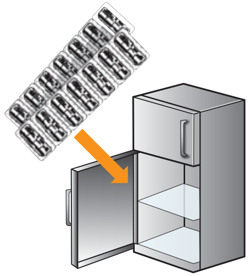


Figure G

Storing Opened Blister Strips

Store opened blister strips in a clean, dry place at room temperature (see **Figure H**), such as a drawer or medicine cabinet.

Opened blister strips must be used within 3 days.

> **Do not** put a blister strip back into the refrigerator after being opened or stored at room temperature.

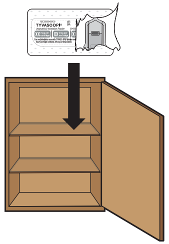


Figure H

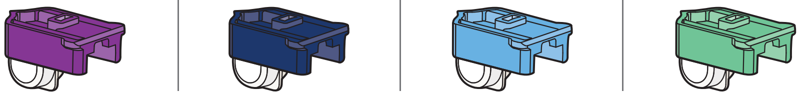
Preparing to Inhale TYVASO DPI

Step 1: Select the TYVASO DPI cartridges for your dose (see Figure I)

Select the TYVASO DPI cartridges for your dose (see **Figure I**).

Note: If using more than 1 cartridge, the cartridges can be used in any order, regardless of cartridge strength.

If your prescribed TYVASO DPI dose is 16 mcg, use...	If your prescribed TYVASO DPI dose is 32 mcg, use...	If your prescribed TYVASO DPI dose is 48 mcg, use...	If your prescribed TYVASO DPI dose is 64 mcg, use...
1 purple cartridge.	**1 dark blue cartridge.**	**1 light blue cartridge.**	**1 light green cartridge.**



If your prescribed TYVASO DPI dose is more than 64 mcg per treatment session, you will need to use more than 1 cartridge to get the right dose.

Example: If your prescribed TYVASO DPI dose is 80 mcg per treatment session, you can use...

1 dark blue cartridge (32 mcg) + **1 light blue cartridge (48 mcg)**

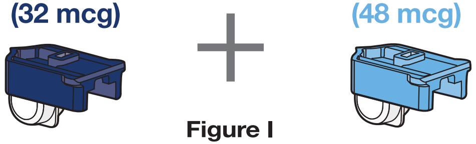


Figure I

Step 2: Tear off 1 strip

Tear along the perforation to remove 1 strip from the blister card (see **Figure J**).

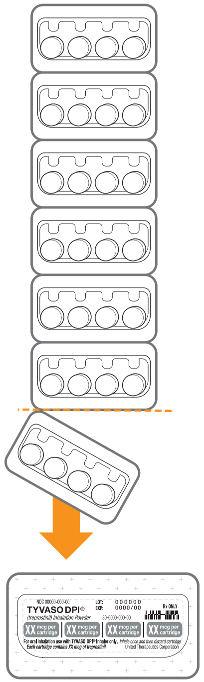


Figure J

Step 3: Check the expiration date on the strip

Check the expiration date on the foil strip label (see **Figure K**).

Do not use the cartridges if the Expiration Date on the strip has passed.

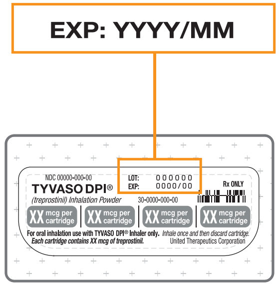


Figure K

Step 4: Remove cartridge(s) from strip

- Remove cartridge(s) from the strip by pushing on the white plastic to push the cartridge out (see **Figure L**).

  Note: Pushing on the cup will not damage the cartridge.
- Make sure to remove the right number of cartridges for your dose.
- After you have removed a cartridge (or cartridges) from the strip, if any unused cartridges remain in the strip, store the strip at room temperature.

  Do not put a blister strip back into the refrigerator after being opened.

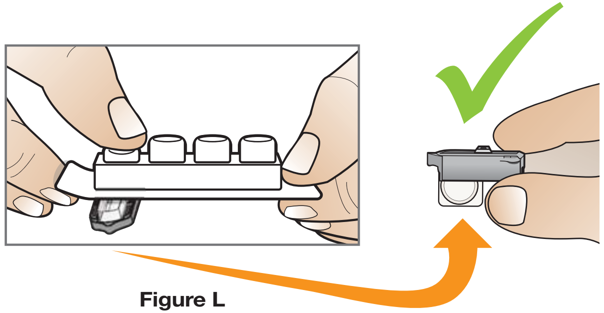
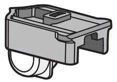


Figure L

Important: If refrigerated, cartridges and inhaler should be left out at room temperature for 10 minutes before use.



ROOM TEMPERATURE

10 mins.

Step 5: Check supplies before continuing

Check that you have the right cartridge(s) for your dose.

Only use one inhaler for multiple cartridges.
Your inhaler lasts for 7 days.

Preparing to Inhale TYVASO DPI (continued)

Step 6: Load a cartridge

Place Inhaler on Flat Surface

Place the inhaler on a flat surface (see **Figure M**).

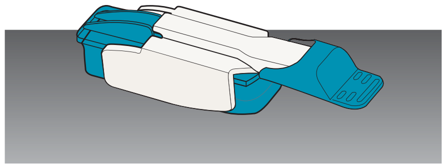


Figure M

Open Inhaler

Open the inhaler by lifting the mouthpiece to an upright (vertical) position (see **Figure N**).

Important: If the cartridge came from a strip stored in the refrigerator (or if you stored the inhaler in the refrigerator), leave the cartridge and inhaler at room temperature for 10 minutes to remove condensation.

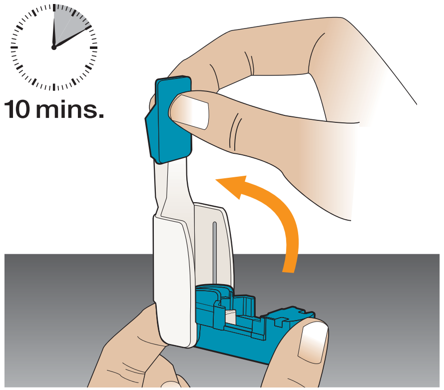


Figure N

Place Cartridge in Inhaler

- Hold the cartridge with the cup facing down (see **Figure O**).
- Line up the cartridge with the opening in the inhaler. The pointed end of the cartridge should line up with the pointed end in the inhaler (see **Figure P**).
- Place the cartridge into the inhaler so that it lies flat.

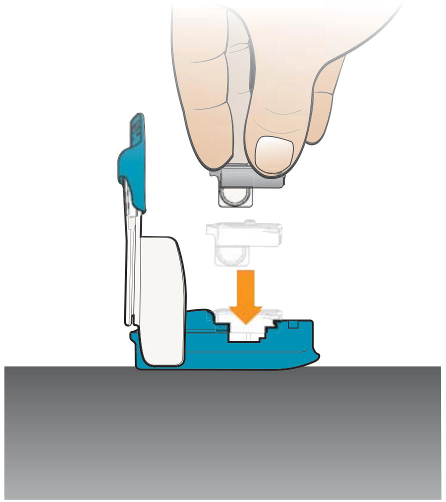


Figure O

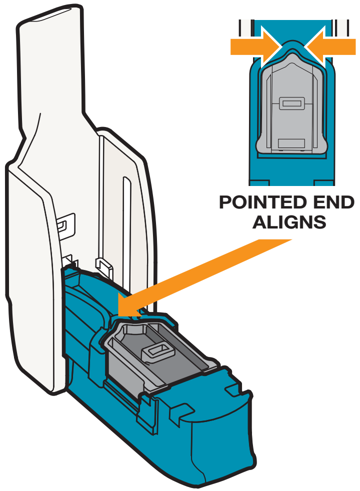


Figure P

Preparing to Inhale TYVASO DPI (continued)

Step 6: Load a cartridge (continued)

Close Inhaler

Close the inhaler (this will open the cartridge). You should feel a snap when the inhaler is closed (see **Figure Q**).

Important: Now that the cartridge is loaded, keep the inhaler level to avoid loss of the TYVASO DPI powder, until it is in your mouth (see **Figure R**).

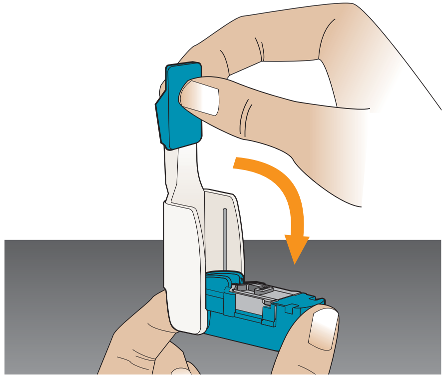


Figure Q

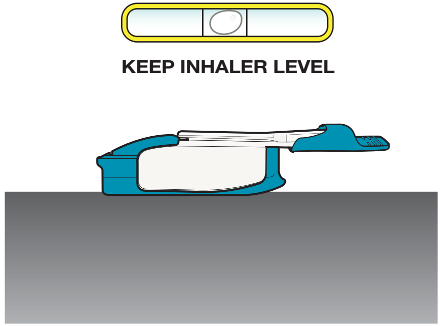


Figure R

Not keeping the inhaler level could cause a loss of TYVASO DPI powder (see Figure S)

If any powder from the cartridge spills:

- Wash your hands right away if the powder comes into contact with your hands,
- Throw away the cartridge into household trash, and
- Repeat Steps 4, 5, and 6 to load a new cartridge

DO NOT turn inhaler upside down. | DO NOT point the mouthpiece down. | DO NOT shake or drop the inhaler.

This can cause a loss of TYVASO DPI powder.

Figure S

Inhaling TYVASO DPI

Before inhaling TYVASO DPI, fully review all parts of Step 7 before you take your dose.

Step 7: Inhale Your Dose

Remove the Mouthpiece Cover (see **Figure T**).

Important: Keep the inhaler level during and after removal of the blue mouthpiece cover to prevent loss of TYVASO DPI powder.

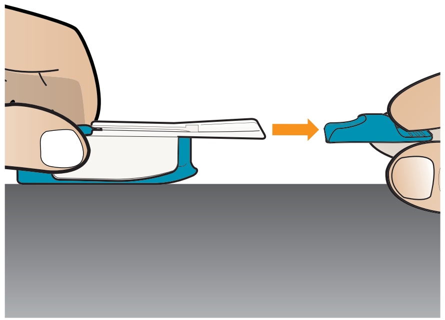


Figure T

Hold Inhaler Near Cheek

While keeping the inhaler level, carefully pick up the inhaler and bring it near your cheek, but not in front of your mouth (see **Figure U**).

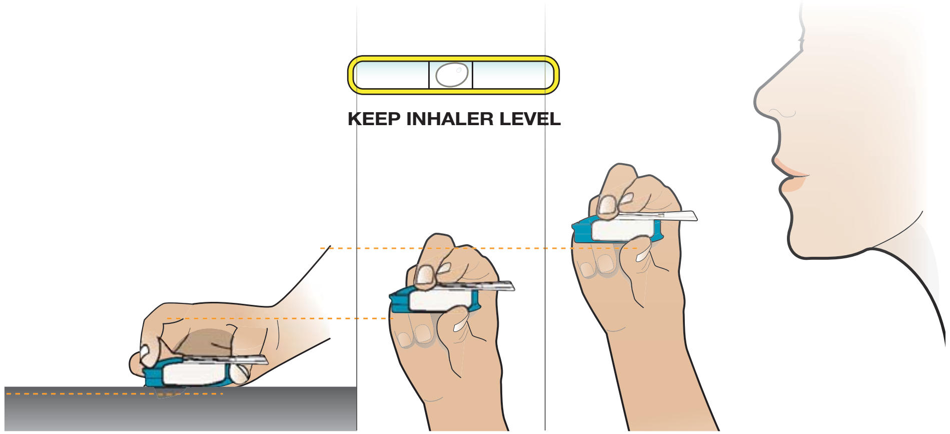


Figure U

Exhale

Holding the inhaler away from your mouth, fully blow out (exhale) (see **Figure V**).

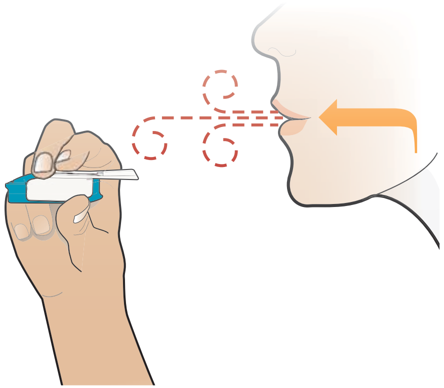


Figure V

Step 7: Inhale Your Dose (continued)

Position Inhaler in Mouth

- Keeping your head level, place the mouthpiece in your mouth and close your lips around the mouthpiece to form a seal.
- Tilt the inhaler slightly downward while keeping your head level (see **Figure W**).

Note: This helps prevent the powder from being blocked by your tongue.

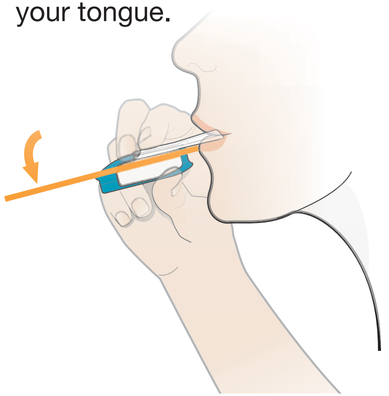


Figure W

Inhale Deeply, Hold Breath, then Exhale

- With your mouth closed around the mouthpiece, **inhale** deeply through the inhaler (see **Figure X**).
- Then remove the inhaler from your mouth and **hold your breath** for as long as you comfortably can (see **Figure Y**).
- Then **blow out** (exhale) and continue to breathe normally (see **Figure Z**).

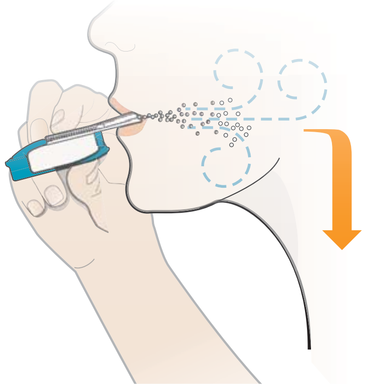


Figure X

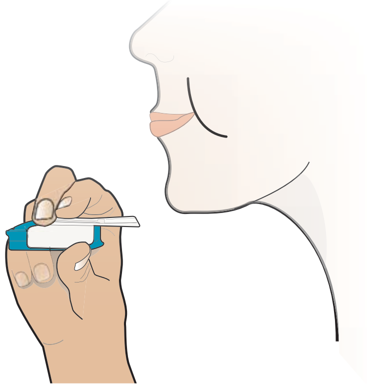


Figure Y

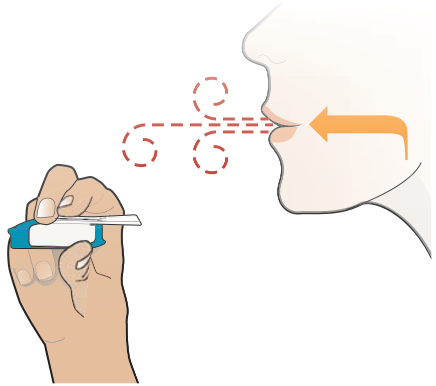


Figure Z

Removing the Used Cartridge

Step 8: Remove the used cartridge

Replace Mouthpiece Cover

Place the mouthpiece cover back onto the inhaler (see **Figure AA**).

Note: This keeps your fingers off the exposed mouthpiece.

Open Inhaler

Open the inhaler by lifting up the mouthpiece to an upright (vertical) position (see **Figure AB**).

Remove Cartridge

- Remove the used cartridge from the blue base (see **Figure AC**).
- The cup should now be in the middle of the used cartridge (see **Figure AD**).

Warning: If any powder from the cartridge spills on your hands, wash your hands right away.

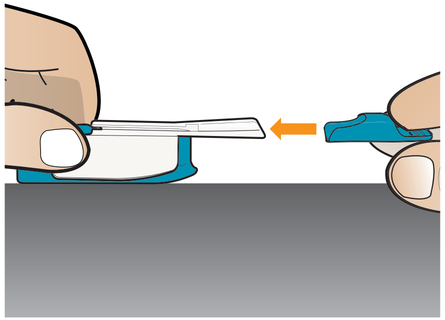


Figure AA

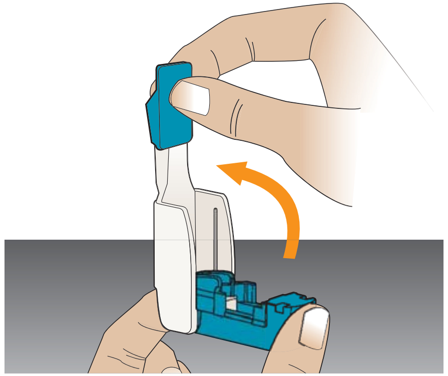


Figure AB

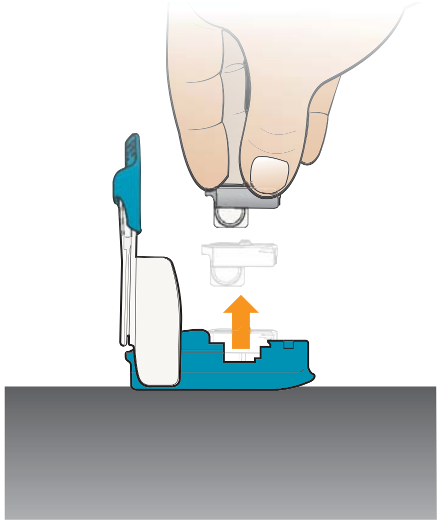


Figure AC

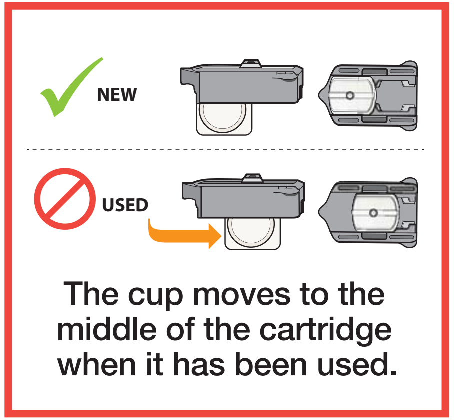


Figure AD

DA0923

LIQ_PH-ILD_00000525

Disposing of TYVASO DPI Cartridges

Step 9: Throw away used cartridge

Throw away the used cartridge in your regular household trash (see **Figure AE**).

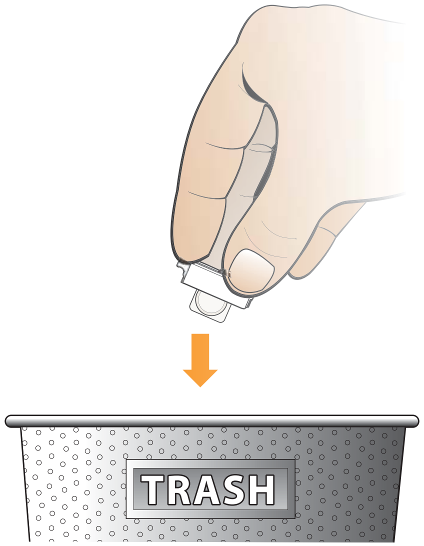


Figure AE

Inhaling Multiple Cartridges of TYVASO DPI

Step 10: Inhaling multiple cartridges (skip if not needed)

If your dose requires you to inhale multiple cartridges, **repeat steps 6 through 9** for each cartridge.

Example: If your prescribed TYVASO DPI dose is 80 mcg per treatment session, you can use one 32 mcg cartridge and one 48 mcg cartridge (see **Figure AF**):

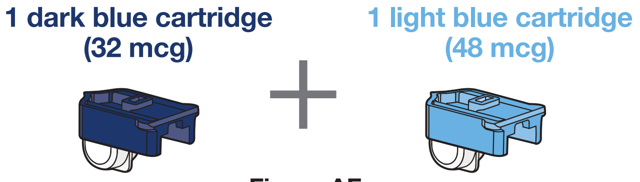


Figure AF

Warning: Be careful not to mix NEW cartridges with used cartridges (see **Figure AG**).

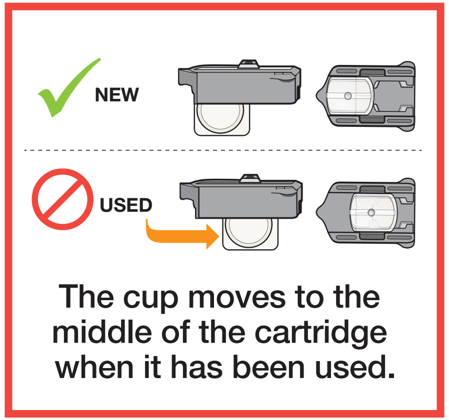


Figure AG

Caring for Your TYVASO DPI Inhaler

Inhaler Care Instructions

Cleaning

After taking your dose, powder residue in the mouthpiece is normal; this will not affect your dose.

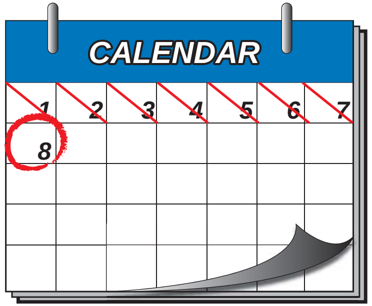
The outside of the inhaler can be wiped with a clean, dry cloth only, if needed.

Never wash the inhaler.
Always keep the inhaler dry.

Use Time

Only use 1 inhaler at a time.
The same inhaler can be used to take 16 mcg, 32 mcg, 48 mcg, or 64 mcg cartridges.

Replace the inhaler after 7 days (see **Figure AH** and **Figure AI**). Keep track of 7 days from when you start using the inhaler with a calendar.



REPLACE
AFTER 7 DAYS

Figure AH

Disposing of Your TYVASO DPI Inhaler

Throw away used inhaler after 7 days of use

After 7 days of use, throw away the used inhaler in your regular household trash (see **Figure AH** and **Figure AI**).

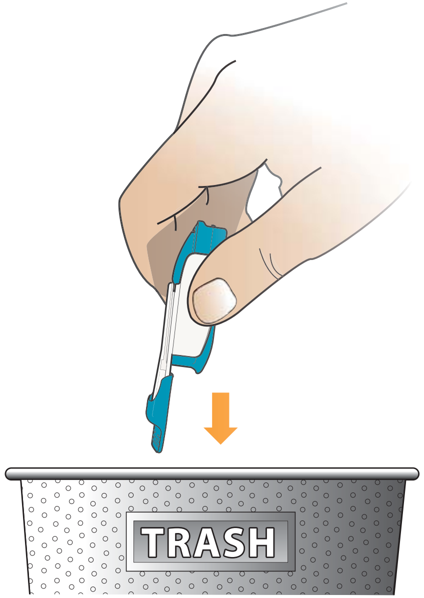


Figure AI

For further questions and information, or to report a problem with your device or any side effects with your TYVASO DPI, please call 1-877-UNITHER (1-877-864-8437).

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: November 2023

TYVASO DPI® is a registered trademark of United Therapeutics Corporation.

Patents: www.tyvasodpi.com/patent

United Therapeutics CORPORATION

Distributed by:
United Therapeutics Corporation
Research Triangle Park, NC 27709
USA

Manufactured by:
MannKind Corporation
Danbury, CT 06810
USA

11/2023 30-1311-006-02

EXHIBIT 30

For Immediate Release

UNITED THERAPEUTICS ANNOUNCES FDA ACCEPTANCE OF TYVASO DPI™ NEW DRUG APPLICATION FOR PRIORITY REVIEW

FDA action expected in October 2021

SILVER SPRING, Md., and RESEARCH TRIANGLE PARK, N.C., Wednesday, June 16, 2021 – United Therapeutics Corporation (Nasdaq: UTHR) today announced that the U.S. Food and Drug Administration (FDA) accepted for priority review the New Drug Application (NDA) for Tyvaso DPI™ (inhaled treprostinil) for the treatment of pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD). United Therapeutics expects the agency's review to be complete in October 2021. FDA also indicated that they have not identified any potential review issues at this time.

Tyvaso DPI is a next-generation dry powder formulation of Tyvaso. If approved, Tyvaso DPI is expected to provide a more convenient method of administration as compared with traditional nebulized Tyvaso therapy.

"The acceptance of the Tyvaso DPI NDA for review represents an important regulatory step toward offering this meaningful new product to both PAH and PH-ILD patients," said Martine Rothblatt, Ph.D., Chairperson and Chief Executive Officer of United Therapeutics. "If approved, Tyvaso DPI will represent yet another path to help us achieve our goal of serving 25,000 patients by the end of 2025."

The NDA includes data from the *BREEZE* study that demonstrated safety and tolerability of Tyvaso DPI in patients with PAH transitioning from Tyvaso® (treprostinil) Inhalation Solution. A separate study in healthy volunteers demonstrated comparable treprostinil exposure between Tyvaso DPI and Tyvaso Inhalation Solution.

In its communications with United Therapeutics, the FDA indicated that approval of the NDA will be subject to an inspection of the Tyvaso DPI manufacturing facility operated by MannKind Corporation; FDA and MannKind have jointly targeted the third quarter of 2021 to complete the inspection.

About Tyvaso DPI™

Tyvaso DPI™ is an investigational drug-device combination therapy comprised of a dry powder formulation of treprostinil and a small, portable, dry powder inhaler. If approved, Tyvaso DPI is expected to provide a more convenient method of administration compared with traditional nebulized Tyvaso® therapy. United Therapeutics is developing Tyvaso DPI under a collaboration and license agreement with MannKind Corporation (Nasdaq: MNKD). Tyvaso DPI incorporates the dry powder formulation technology and Dreamboat® inhalation device technology used in MannKind's Afrezza® (insulin human) Inhalation Powder product, which was approved by the FDA in 2014.

United Therapeutics and MannKind are also developing BluHale®, a Bluetooth-connected accessory for the Tyvaso DPI inhaler with a companion mobile application intended to help the patient track information about inhaler use.

About the *BREEZE* and healthy volunteer PK studies

The *BREEZE* study was a single-sequence study in which 51 subjects on a stable regimen of Tyvaso Inhalation Solution were transitioned to Tyvaso DPI at a corresponding treprostinil dose. The primary objective of the study was to evaluate the safety and tolerability of Tyvaso DPI during a three-week treatment phase in PAH patients previously treated with Tyvaso Inhalation Solution.

Secondary objectives of the study were to evaluate: (1) the systemic exposure and pharmacokinetics of treprostinil when delivered as Tyvaso Inhalation Solution and Tyvaso DPI; (2) six-minute walk distance (**6MWD**) at study entry and after three weeks of treatment with Tyvaso DPI; (3) the long-term safety and tolerability of Tyvaso DPI during an optional extension phase (**OEP**) in patients previously treated with Tyvaso Inhalation Solution; (4) patient satisfaction with and preference for inhaled treprostinil devices assessed at study entry when patients were using Tyvaso Inhalation Solution and after three weeks using Tyvaso DPI; and (5) patient-reported PAH symptoms and impact (**PAH-SYMPACT®**) assessed at study entry when patients were using Tyvaso Inhalation Solution and after three weeks using Tyvaso DPI.

Primary safety and tolerability objective. Transition from Tyvaso Inhalation Solution to Tyvaso DPI was safe and well tolerated. Forty-nine out of 51 patients (96%) completed the treatment phase and there were no study drug related adverse events. Most adverse events experienced during the study were mild to moderate in severity and occurred at severities and frequencies consistent with those seen in other inhaled treprostinil studies in patients with PAH.

Secondary objectives. Three weeks after switching from Tyvaso Inhalation Solution to Tyvaso DPI, patients in the *BREEZE* study demonstrated:

- Improvements in 6MWD compared to baseline. These improvements in 6MWD compared to baseline were sustained in the OEP through the data cut-off date.
- Improvements in overall satisfaction with the Tyvaso DPI inhaler compared to the Tyvaso Inhalation Solution nebulizer at baseline using an internally developed satisfaction and preference questionnaire.
- Improvement in patient-reported outcomes using the validated PAH-SYMPACT questionnaire.

Optional extension phase. Subjects in *BREEZE* were given the opportunity to continue in an OEP. All subjects who completed the treatment phase (49/51) elected to continue in the OEP.

***BREEZE* PK observations.** The *BREEZE* study demonstrated comparable PK between Tyvaso inhalation solution and Tyvaso DPI in PAH patients.

Detailed data from the *BREEZE* study will be presented in upcoming publications and scientific conferences.

Healthy volunteer PK study. The healthy volunteer pharmacokinetic (**PK**) study was a randomized six-period, six-sequence crossover study of three dose levels of Tyvaso DPI and three dose levels of Tyvaso Inhalation Solution in 36 healthy volunteers. The primary objective of the study was to evaluate the systemic exposure and PK of treprostinil administered as Tyvaso DPI and Tyvaso Inhalation Solution. Secondary objectives of the study evaluated the safety and tolerability of Tyvaso DPI.

Study results. Subjects demonstrated comparable systemic treprostinil exposure for each corresponding Tyvaso DPI and Tyvaso Inhalation Solution dose level. Between-subject variability for both $AUC_{0\text{-}5h}$ and C_{max} was approximately 50% less for Tyvaso DPI compared to Tyvaso Inhalation Solution, suggesting a more precise dosing profile for Tyvaso DPI relative to nebulized Tyvaso.

Safety. The adverse event profile for Tyvaso DPI in healthy volunteers was consistent with known prostacyclin effects and previous studies of Tyvaso Inhalation Solution.

Detailed data from the healthy volunteer PK study will be presented in upcoming publications and scientific conferences.

About PH-ILD

Interstitial lung disease (**ILD**) is a group of lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs within the lungs. Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs, and the condition can present with a wide range of symptoms, including shortness of breath with activity, labored breathing and fatigue. Pulmonary hypertension (**PH**) frequently complicates the course of patients with interstitial lung disease and is associated with worse functional status measured by exercise capacity, greater supplemental oxygen needs, decreased quality of life, and worse outcomes.

An estimated 30,000 patients in the United States may suffer from PH-ILD, which is included within Group 3 of the World Health Organization (**WHO**) classification of PH. Only Tyvaso Inhalation Solution is approved to treat patients with this disease.

About PAH

Also known as World Health Organization (**WHO**) Group 1 Pulmonary Hypertension, Pulmonary arterial hypertension (**PAH**) is life-threatening high blood pressure in the arteries of the lungs, affecting the ability of the heart and lungs to work properly in afflicted patients. PAH is a serious, progressive disease for which there is no cure.

About TYVASO® (treprostinil) Inhalation Solution

INDICATION

TYVASO (treprostinil) is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

  The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

  While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- TYVASO is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, TYVASO may produce symptomatic hypotension.
- TYVASO inhibits platelet aggregation and increases the risk of bleeding.

- Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of TYVASO with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.
- Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality. There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.
- Safety and effectiveness in pediatric patients have not been established.
- Across clinical studies used to establish the effectiveness of TYVASO in patients with PAH and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

- Pulmonary Arterial Hypertension (WHO Group 1)
  In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most common adverse reactions seen with TYVASO in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%). In addition, adverse reactions occurring in ≥4% of patients were dizziness and diarrhea.

- Pulmonary Hypertension Associated with ILD (WHO Group 3)
  In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse reactions were similar to the experience in studies of PAH.

Please see Full Prescribing Information, the TD-100 and TD-300 TYVASO® Inhalation System Instructions for Use manuals, and other additional information at www.tyvaso.com or call 1-877-UNITHER (1-877-864-8437).

United Therapeutics: Enabling Inspiration
United Therapeutics Corporation focuses on the strength of a balanced, value-creating biotechnology model. We are confident in our future thanks to our fundamental attributes, namely our obsession with quality and innovation, the power of our brands, our entrepreneurial culture, and our bioinformatics leadership. We also believe that our determination to be responsible citizens – having a positive impact on patients, the environment, and society – will sustain our success in the long term.

Through our wholly owned subsidiary, Lung Biotechnology PBC, we are focused on addressing the acute national shortage of transplantable lungs and other organs with a variety of technologies that either delay the need for such organs or expand the supply. Lung Biotechnology is the first public benefit corporation subsidiary of a public biotechnology or pharmaceutical company.

Please visit unither.com to learn more.

Forward-looking Statements

Statements included in this press release that are not historical in nature are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, statements relating to the timing and outcome of FDA review of our NDA for Tyvaso DPI, our goal of serving 25,000 patients by 2025, the potential benefits of Tyvaso DPI for patients, our ability to create value and sustain our success in the long-term, and our efforts to develop technologies that either delay the need for transplantable organs or expand the supply of transplantable organs. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of June 16, 2021 and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason.

For Further Information Contact:
Dewey Steadman at (202) 919-4097
Email: ir@unither.com

* * *

EXHIBIT 31

Robustness of YUTREPIA™, a Dry-Powder Inhaled Formulation of Treprostinil, in Patient Misuse Scenarios

Savan Patel[1], Jason Prabel[1], Drew MacLennan[1], Gavin Rosen[1]

[1]Liquidia Technologies, Inc., Morrisville, NC, USA.

Background

The current standard of care for inhaled treatment of pulmonary arterial hypertension (PAH) is a nebulized treprostinil solution administered four times a day (QID). A robust and easily used alternative inhaled treprostinil would improve patient compliance and quality of life.

Investigational drug, YUTREPIA™ (LIQ861) is a novel dry-powder formulation of treprostinil designed using proprietary PRINT® Technology. The PRINT® process enables the development of drug particles that are precise and uniform in size, shape, and composition. YUTREPIA particles are monodisperse and have minimal agglomeration allowing efficient delivery to the lungs by a simple capsule-based, dry powder inhaler (DPI, Plastiape RS00 Model 8) with low resistance and high robustness to potential patient misuse.

In vitro aerosol performance results are presented to support the robustness of the dosage form to potential patient misuse scenarios[1].

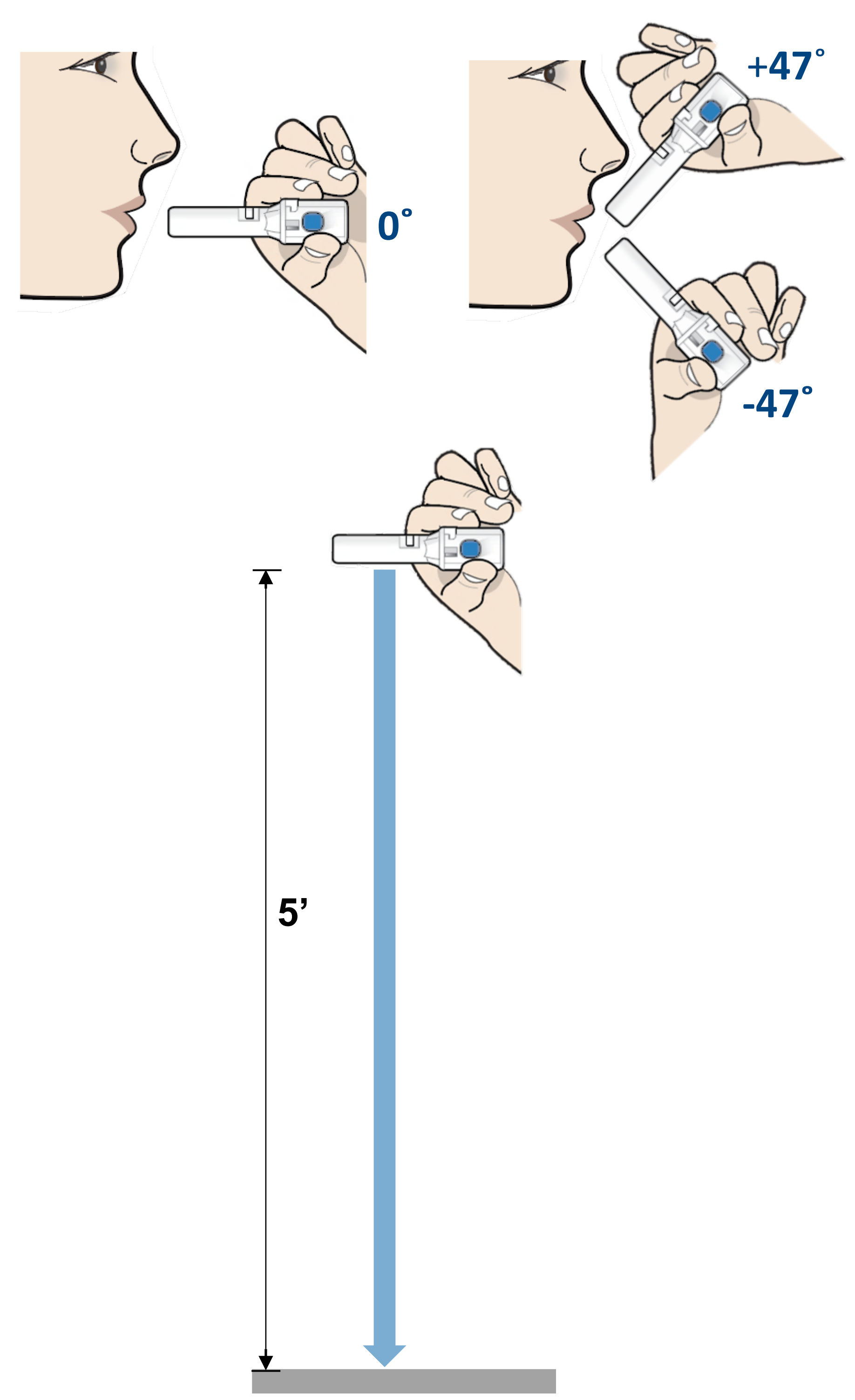
Methods

Liquidia studied the effect of varying DPI orientation on YUTREPIA dosing *in vitro* by measuring aerosol performance at inhaler angles of -47°, 0°, and +47° relative to horizontal after loading and puncturing the capsule within the device.

The effects of patients accidentally dropping the DPI were investigated *in vitro* using a drop height of 5 feet to approximate mouth distance from the ground and simulate two potential patient misuse scenarios. The first scenario investigated the effects of dropping the DPI with the mouthpiece facing down after loading and puncturing the capsule. The second scenario explored the effects of dropping the DPI with the mouthpiece facing up after loading but before puncturing the capsule.

Each study used capsules containing doses of 26.5 mcg and 106 mcg of YUTREPIA. These doses bracket the YUTREPIA capsule strength range as the lowest and highest strengths currently available and results are considered to support all four dosage strengths.

Standard USP <601> *in vitro* methods assessed aerosol performance. Emitted dose (ED) was measured using a Dosage Unit Sampling Apparatus (DUSA); Aerodynamic Particle Size Distribution (APSD) results were collected using a Next Generation Impactor (NGI).

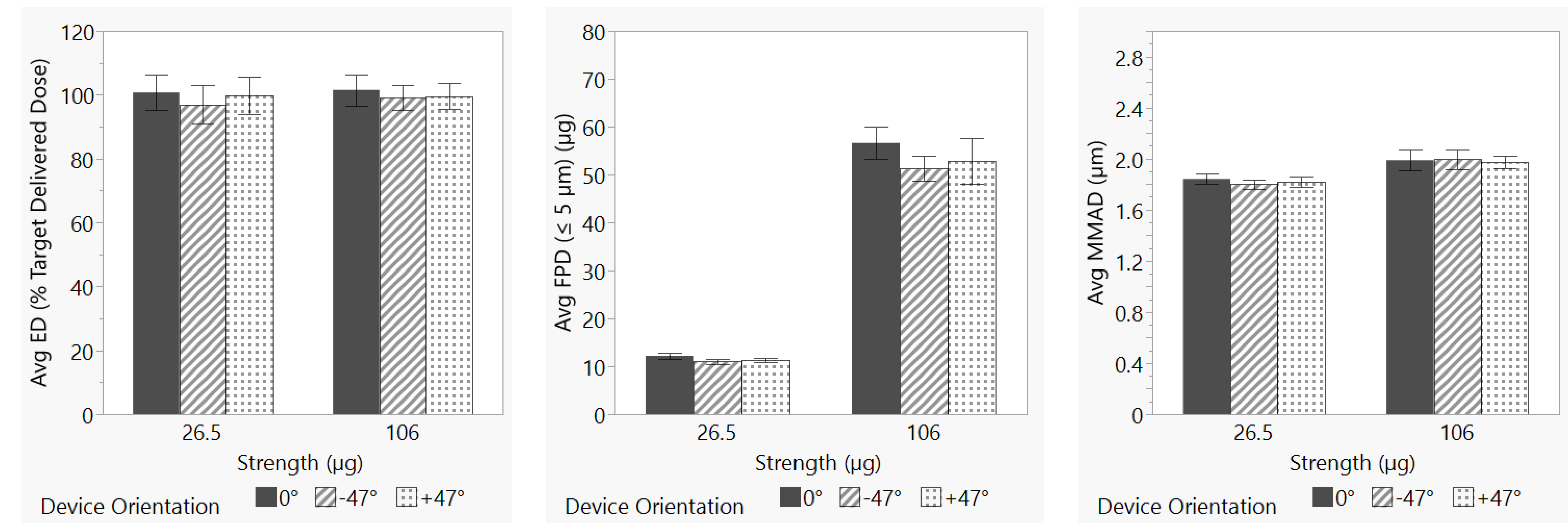


1. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control [published correction appears in Respir Med. 2012 May;106(5):757. DelDonno, Mario [corrected to Del Donno, Mario]]. *Respir Med*. 2011;105(6):930-938. doi:10.1016/j.rmed.2011.01.005

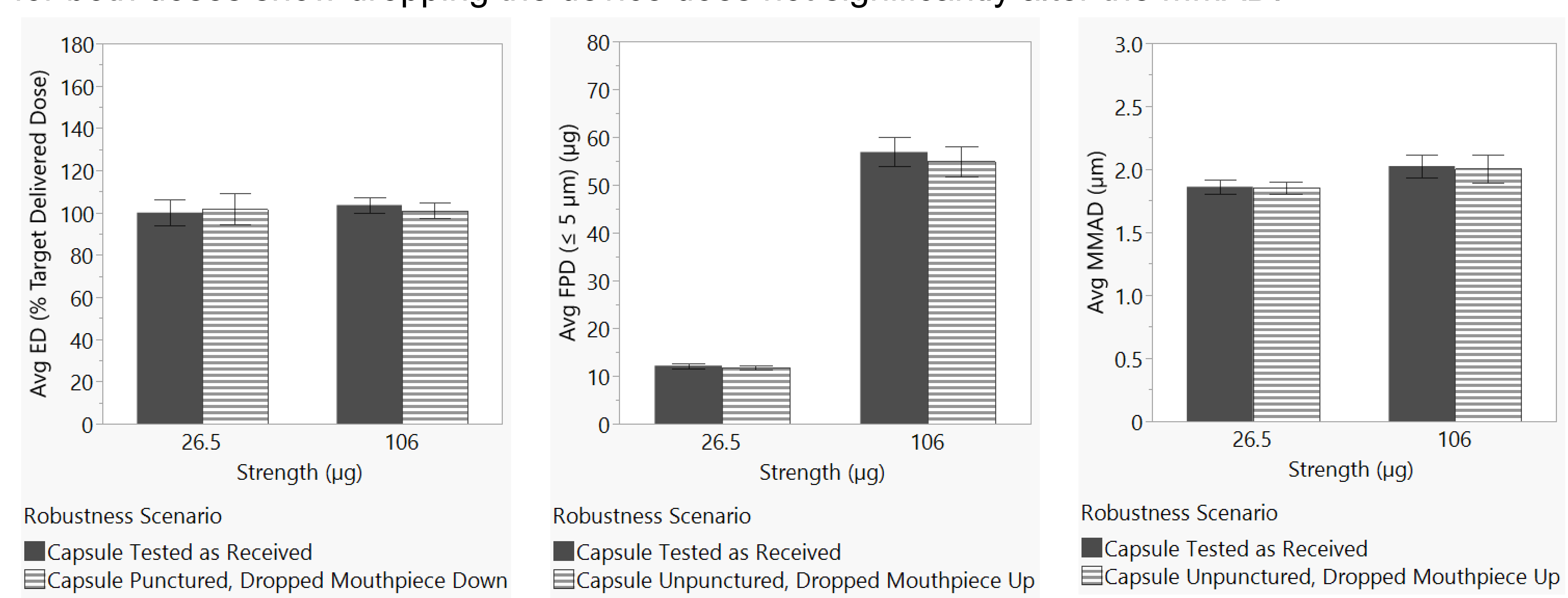
Results

Emitted Dose (ED), Fine Particle Dose (FPD), and Median Mass Aerodynamic Diameter (MMAD) demonstrate consistent *in vitro* exposure while varying device orientation and dropping the inhaler before or after puncturing the capsule.

DUSA and APSD assessments for 26.5 mcg and 106 mcg doses show no significant differences in ED and FPD at -47˚ and +47˚ compared to results at 0˚. APSD results show MMAD is not significantly altered and is ≤2.0 µm for both dosage strengths at all orientations.



DUSA and APSD evaluations for 26.5 mcg and 106 mcg doses show dropping the DPI from 5 feet before or after puncturing the capsule has no significant effect on ED and FPD. APSD results for both doses show dropping the device does not significantly alter the MMAD.

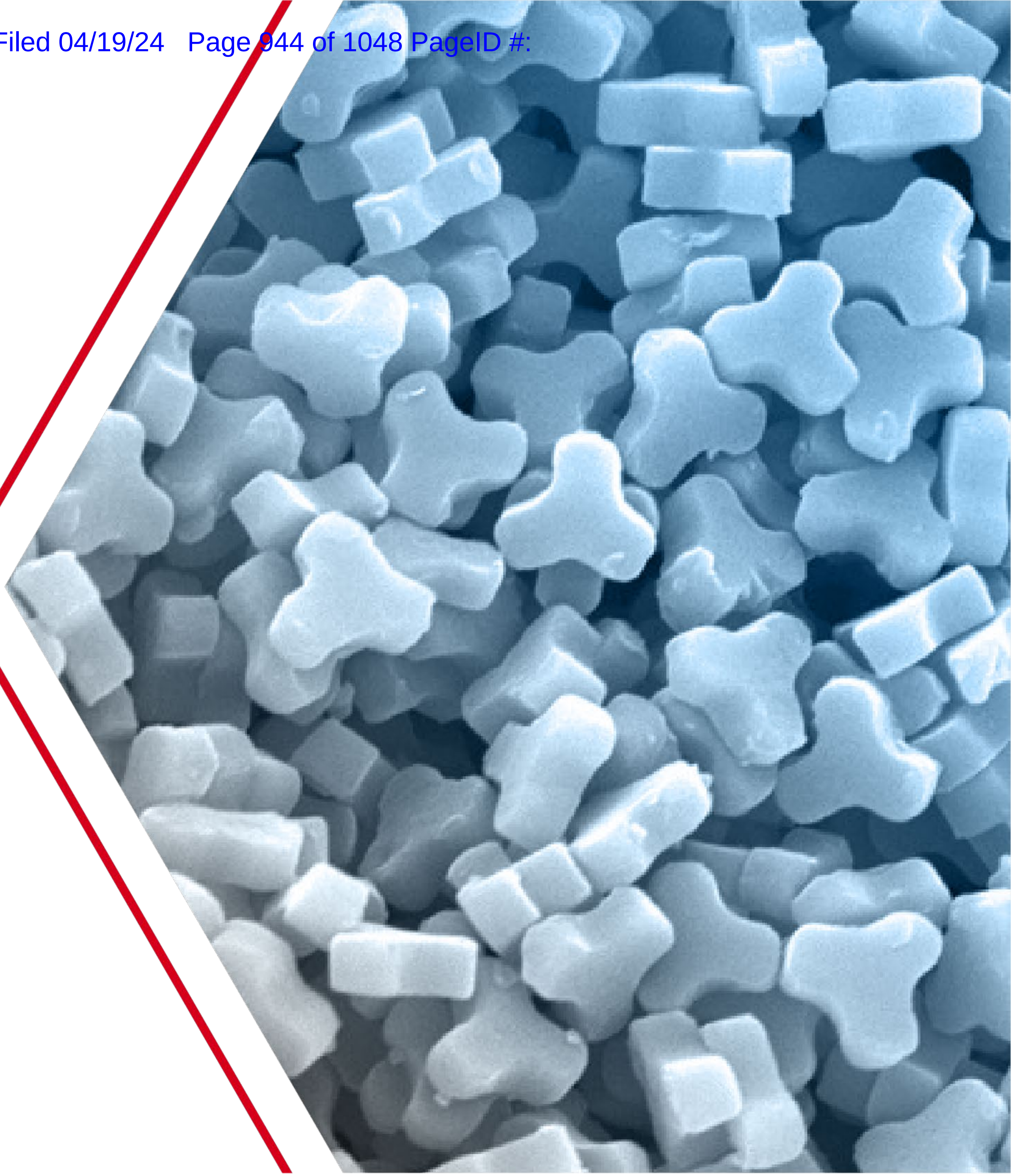


Conclusions

The aerosol performance of YUTREPIA is not affected by real-world patient misuse scenarios such as varying the inhalation orientation or dropping the DPI. The robustness of YUTREPIA results in consistent drug exposure to patients.

EXHIBIT 32

Liquidia CORPORATION



Corporate Overview

June 20, 2022

Forward-Looking Statements

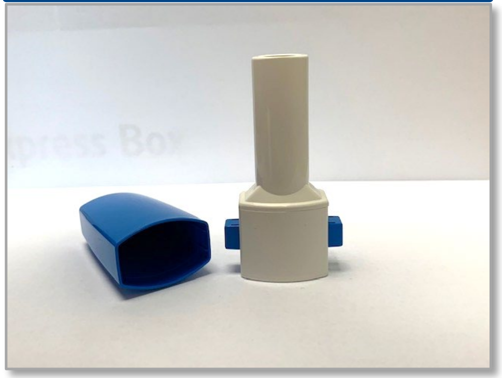
This presentation includes, and our response to questions may include, forward-looking statements within the meaning of the federal securities laws, including Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements contained in this presentation other than statements of historical facts, including statements regarding our future results of operations and financial position, our strategic and financial initiatives, our business strategy and plans and our objectives for future operations, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “estimate,” “expect,” “intend,” “may,” “will” and similar expressions are intended to identify forward-looking statements. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy, short-term and long-term business operations and objectives and financial needs. These forward-looking statements include statements regarding our operating results, clinical trials, clinical studies and other clinical work (including the funding therefor, anticipated patient enrollment, safety data, study data, trial outcomes, timing or associated costs), regulatory applications and NDA submission contents and timelines, the potential for FDA final approval of the NDA for YUTREPIA™ (treprostinil) inhalation powder, previously referred to as LIQ861, the timeline or outcome related to our patent litigation pending in the U.S. District Court for the District of Delaware or the *inter partes review* with the PTAB or any appeals related thereto, the issuance of patents by the USPTO, our ability to execute on our strategic or financial initiatives and the impact of the coronavirus (COVID-19) pandemic on our Company. Moreover, we operate in a very competitive and rapidly changing environment and our industry has inherent risks. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the future events and trends discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that future results, levels of activity, performance, achievements or events and circumstances reflected in the forward-looking statements will occur. We are under no duty to update any of these forward-looking statements after the date of this presentation to conform these statements to actual results or revised expectations, except as required by law. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. This presentation includes long-term goals that are forward-looking, are subject to significant business, economic, regulatory and competitive uncertainties and contingencies, many of which are beyond our control and are based upon assumptions with respect to future decisions, which are subject to change. Actual results will vary, and those variations may be material. Nothing in this presentation should be regarded as a representation by any person that these goals will be achieved, and we undertake no duty to update our goals.

Transformational time for Liquidia

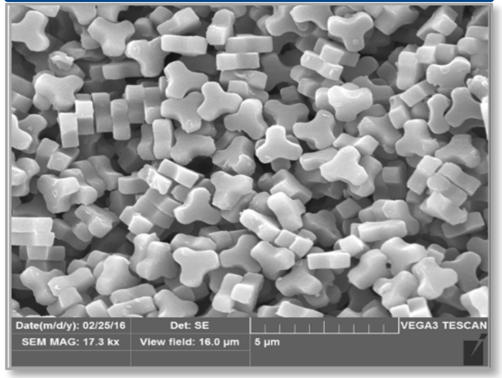
A growing company focused on PAH and PH-ILD

- **Established commercial footprint with RareGen merger**
  - Treprostinil Injection, generic for Remodulin®
  - Enabled both Intravenous & Subcutaneous administration
- **Received Tentative FDA Approval of YUTREPIA™ (treprostinil) inhalation powder**
  - Confirmed full draft labeling in November 2021
  - Seeking resolution of ongoing patent litigation with UTHR
- **Prepared to expand commercial efforts**
  - Building on core team with deep experience in PAH
  - Fortified balance sheet to enable launch when ready
  - Per FDA guidance, can request PH-ILD indication in 1H2024 without need for additional studies in sNDA

YUTREPIA™ DPI Device



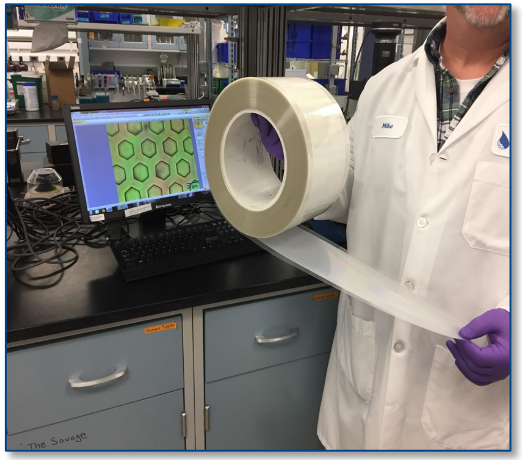
Dry Powder Treprostinil Developed Using PRINT



Pulmonary Arterial hypertension (PAH); Pulmonary Hypertension with Interstitial Lung Disease (PH-ILD)
Remodulin® is a registered trademark of United Therapeutics Corporation (UTHR)

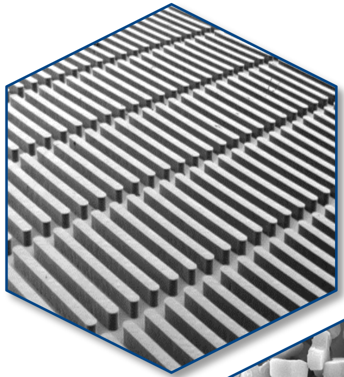
Propriety Advantage In PRINT® Technology Platform

Particle Replication In Non-wetting Templates (PRINT®) for precise particle engineering

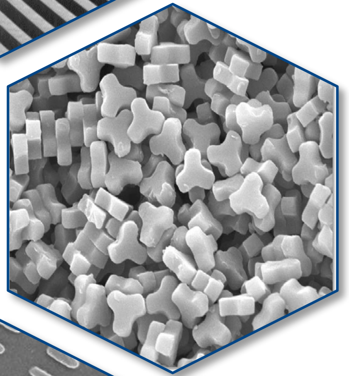


- **Applicable to any therapeutic area, molecule, and route**
- **Proven science and scalable manufacturing**
- **FDA approved In-House GMP Facility**

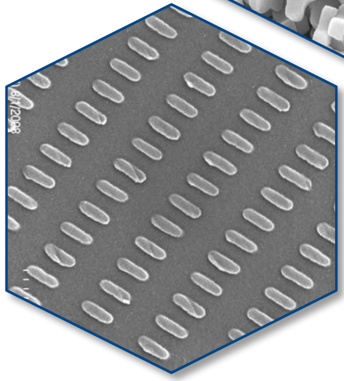
- Utilizes manufacturing techniques from the microelectronics industry to manufacture drug product particles with precise size, shape, weight, and chemical composition to target minute absorptive lung surfaces



Milliscale
implants
sustained release



Microscale
inhaled
dry powder



Nanoscale
co-delivery
immunomodulation

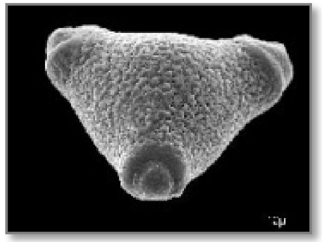
Engineered Particles to Enhance Delivery to Lower Lung

Monodisperse Particles with Precise Geometries for Inhalation

Shape influences aerodynamic performance

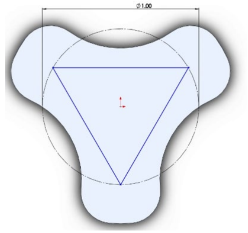
Inspired by nature

Pollen Particle



Eperua schomburgkiana

YUTREPIA PRINT particles

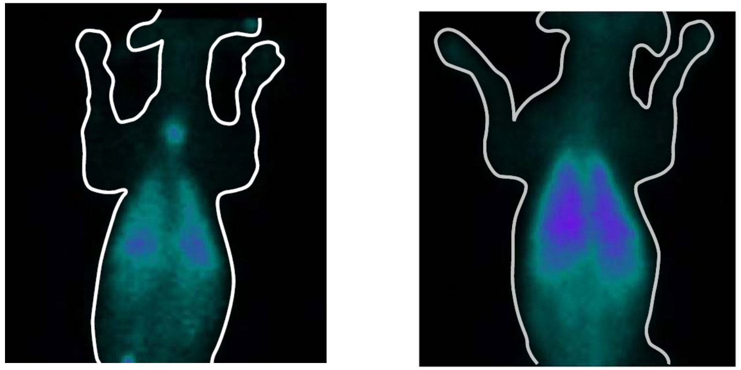


- **1.3 µm MMAD**
- **Trefoil shape**

Size influences alveolar deposition

Particle sizes ≤ 5 µm are respirable but deposit differently

4.6 µm MMAD particle | **1.3 µm MMAD particle**



Tc^{99} scintigraphy of PRINT particles in canine model[1]

Provides preferential delivery to alveolar region and less upper airway deposition

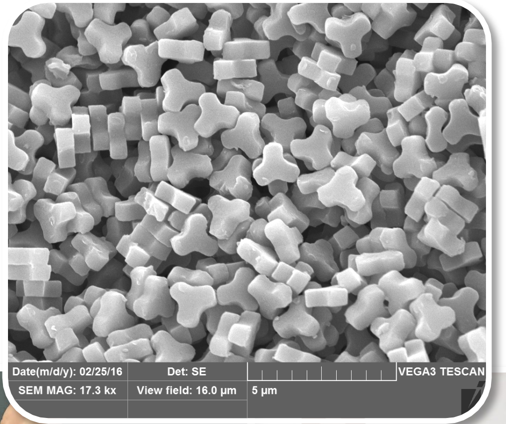
Median mass aerodynamic diameter (MMAD); 1. Garcia A, et al., Journal of Drug Delivery Volume 2012, Article ID 941243

YUTREPIA™ (treprostinil) inhalation powder

Engineered to enhance delivery to lower lung of PAH patients

FDA Tentative Approval on November 8, 2021[1]

- **Approved based on safety data from INSPIRE trial (n=121)**
- **Demonstrated comparable bioavailability of 9 breaths Tyvaso® with only 2 breaths from a single capsule**
- **Administered doses comparable to 24 breaths of Tyvaso® 4x daily**
- **No Maximum Tolerated Dose identified**
- **IP position protected with patent claims into 2037**
  - Includes claims that cover the use of ~100 to 300mcg dry-power treprostinil to treat pulmonary hypertension[2]
- **Potential commercial launch subject to ongoing IP litigation with UTHR**



1. Pulmonary Hypertension (PH), 1. Nov 8, 2021 press release; 2. Aug 28, 2020 press release; Tyvaso® is a registered trademarks of United Therapeutics Corporation (UTHR)

YUTREPIA™ Checks All the Boxes for a Preferred Product Profile

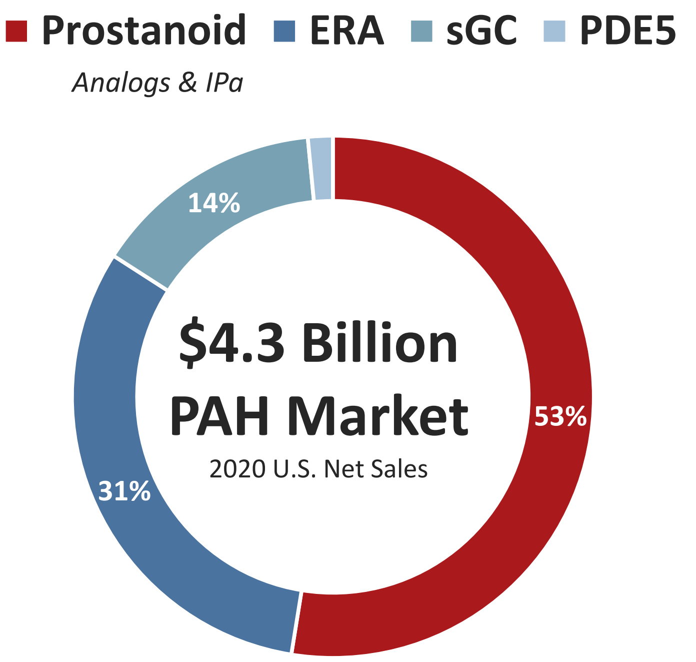
We believe YUTREPIA is positioned to become the prostacyclin of first-choice

		YUTREPIA™
Portability	Replace burden of nebulizers with palm-sized, simple device; potential for earlier use	✓
Tolerability	Reduce systemic toxicity when adding prostacyclin to naïve patients or escalating dose	✓
Titratability	Demonstrate safe titration to doses comparable to 24 breaths Tyvaso, 4x day	✓
Durability	Potential to treat patients longer before transitioning to more invasive parenteral forms	✓
Storage	Store at room temperature for product lifetime	✓
Device Resistance	Accommodate wide range of lung capacities by using low resistance device	✓
Device Position	Avoid product spillage by using capsule-based drug and trusted device	✓

Tyvaso® is a registered trademarks of United Therapeutics Corporation (UTHR)

YUTREPIA Has Potential to Rapidly Garner Significant Market Share

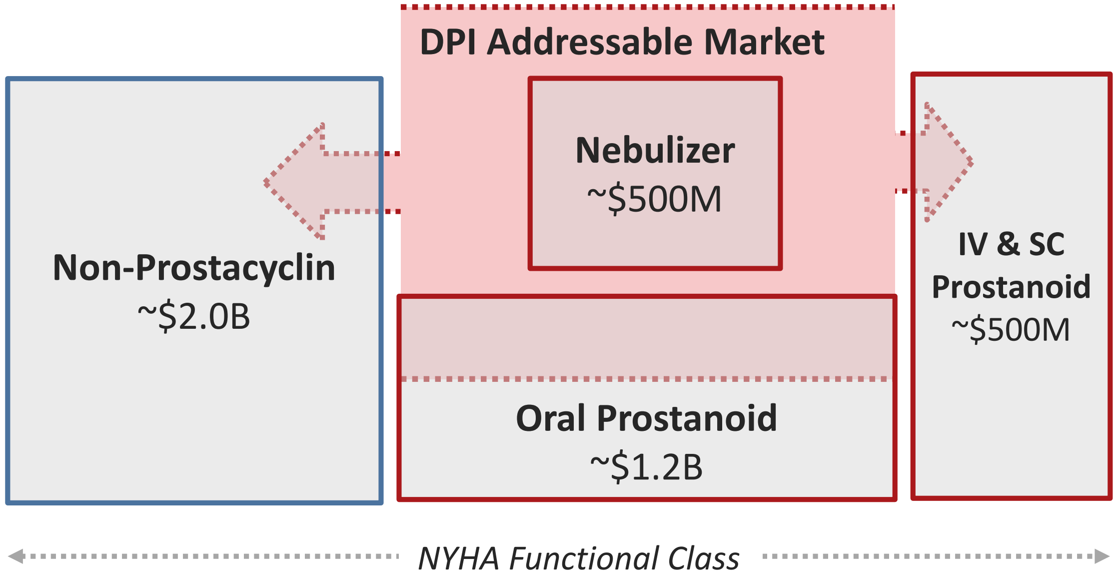
Goal of prostanoid therapy is to dose to highest tolerable level to provide symptomatic benefit



>50% of prostanoid market included treprostinil formulations ($1.2 billion)

Expect paradigm shift in treatment as DPIs grow inhaled market in PAH

+ Fewer systemic toxicities with targeted lower lung delivery
+ Portability, Tolerability, Titratability, Durability
+ Cannibalize nebulizers, capture oral share, earlier use, & delay parenteral



U.S. sales sourced from 2020 10-K SEC filings from United Therapeutics, JNJ, Gilead, Bayer, Merck; New York Heart Association (NYHA)

WHO Group 1 Represents a Significant Initial Market Opportunity

Additional WHO Groups Provide Market Expansion Opportunities

Pulmonary Hypertension

WHO Group 1
Due to PAH

PAH
~45,000 patients
2 local options (nebulized)

Oral	orenitram treprostinil EXTENDED-RELEASE TABLETS	Uptravi selexipag
IV/SC	REMODULIN (treprostinil) Injection	epoprostenol
Nebulized	TYVASO (treprostinil) INHALATION SOLUTION	INHALED Ventavis (iloprost) INHALATION SOLUTION

WHO Group 2
Due to Left Heart Disease

WHO Group 3
Due to Chronic Lung Disease

PH-ILD
~30,000 patients
Only 1 approved Rx

PH-COPD
- ***~100,000 pts with No Approved Treatments***
- *1 nebulized pivotal trial on-going*[2]

TYVASO (treprostinil) INHALATION SOLUTION
For PH-ILD (FDA 2021)[1]

WHO Group 4
Due to CTEPH

WHO Group 5
Due to unclear MOA

Not PH

IPF
Idiopathic Pulmonary Fibrosis

IPF
- ***~100,000 pts with No Inhaled Treatments***
- *1 nebulized pivotal trial on-going*[3]

Our Portfolio

Tentative FDA approval YUTREPIA™

Potential 1st line prostacyclin in PAH

Potential future indications for YUTREPIA

Clinical data support PH-ILD indication once Tyvaso data exclusivity expires March 2024

Potential future indications for YUTREPIA

Pulmonary Arterial Hypertension (PAH); Pulmonary Hypertension (PH); Interstitial Lung Disease (ILD); Chronic Obstructive Pulmonary Disorder (COPD); Idiopathic Pulmonary Fibrosis (IPF); Patient estimates sourced by combination of Liquidia internal estimate and public statements by United Therapeutics (Feb 2022);
1. https://www.nejm.org/doi/full/10.1056/NEJMoa2008470; 2. https://clinicaltrials.gov/ct2/show/NCT03496623; 3. https://www.clinicaltrials.gov/ct2/show/NCT04708782

Deep Experience Within PAH, Rare Disease and Inhaled Products

Roger Jeffs
Chief Executive Officer

- Former UTHR Executive (18 yrs) including President/COO (2001-14) & co-CEO (2015-16)
- Led R&D, secured FDA approval of 6 rare diseases products at United Therapeutics

Rajeev Saggar, M.D.
Chief Medical Officer

Announced Jun 20th with July 18, 2022 start

- 20+ yrs practicing pulmonologist with 60+ peer-reviewed publications incl. PAH & PH-ILD
- Served as Interim Chief of Div. of Pulmonary Critical Care at Univ. of Arizona, College of Medicine; Medical Director of PH & Fibrosis Pgms and Lung Transplant at Banner University Medical Center

Scott Moomaw
Senior VP Commercial

- Former UTHR VP Marketing (5 yrs) responsible for Remodulin®, Tyvaso® & Orenitram®
- Co-founded RareGen as COO (2018) launching generic Treprostinil Injection

Matt Snow
Vice President National Sales

- Former UTHR commercial leader (7 yrs) in multiple roles in sales leadership and training
- Launched rare disease products for SOBI (National Sales Dir.) & INSMED (Regional Lead)

Existing Commercial Presence in PAH with Treprostinil Injection

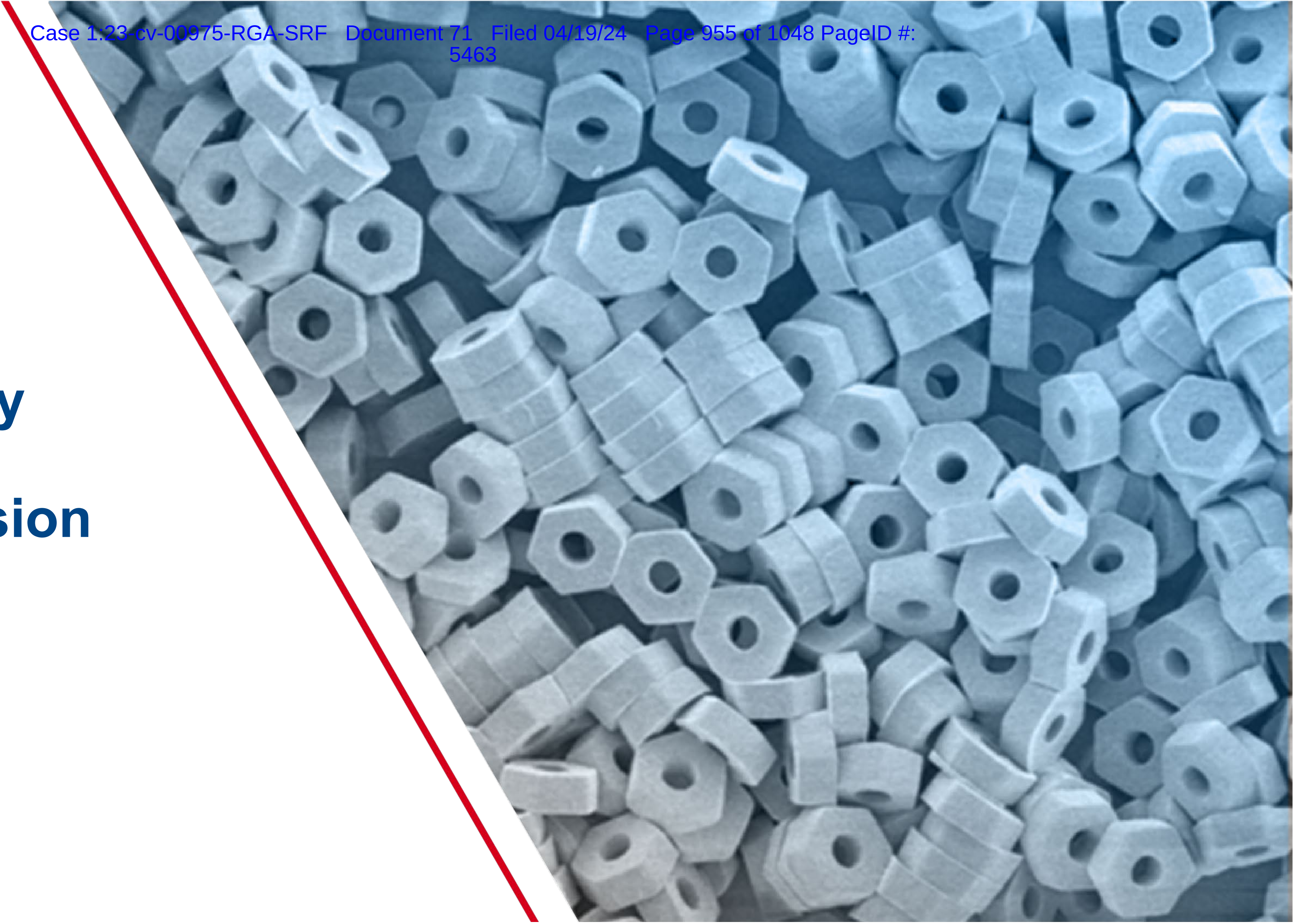
Specialty field sales team & co-pay programs replicate experience with branded drug

- ✓ Equivalent product
- ✓ Reliable Supply
- ✓ Seamless Service
- ✓ Lower Price

- 400+ unique prescribers switched patients from brand to generic
- More than doubled active patients after SC route added (Apr’21)
- ~500 active treprostinil injections patients in 1Q2022
- Planning for growth as payer generic mandates enforced
- Additional larger payers plan to implement mandates in 2022

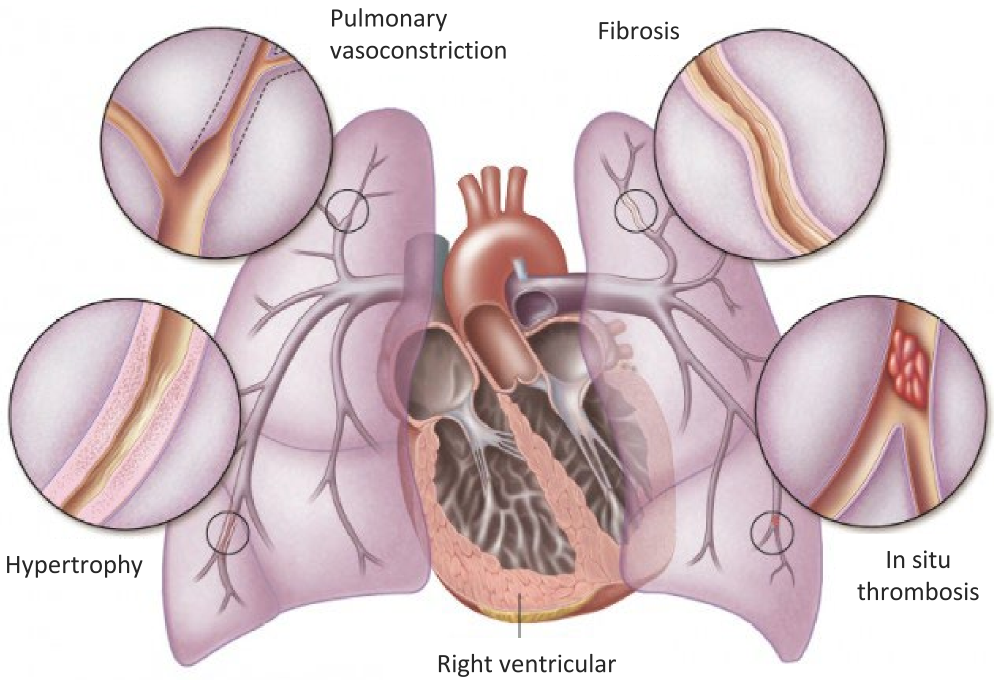
Liquidia Data from Specialty Pharmacies as of March 17, 2022

Pulmonary Arterial Hypertension



Currently Focused On Maximizing the Benefits of Prostenoid Treatment of PAH

WHO Group 1 (Pulmonary Arterial Hypertension)



Abnormal changes in arteries of the lungs increase pressure in pulmonary arteries that leads to remodeling of the right ventricle (RV)

Multiple pathways are involved in pathogenesis

Prostacyclin Deficiency

- **Prostacyclin inhibits platelet aggregation, relaxes smooth muscle, and vasodilates the pulmonary arteries**

Nitric Oxide Deficiency

- Nitric Oxide (NO) leads to vasodilation by increasing cGMP levels

Endothelin Overexpress

- Endothelin (ET-1) mediates vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation

World Health Organization (WHO)
Farber *Eur Respir Rev* 2016; Lang *Eur Respir Rev* 2014; Channik *Advances in Pulmonary Hypertension Spring,* 2002, Yen-Chun Lai et al. Circ Res. 2014;115:115-130

Current Options Are Suboptimal and Potentially Delay Benefit of Prostacyclin

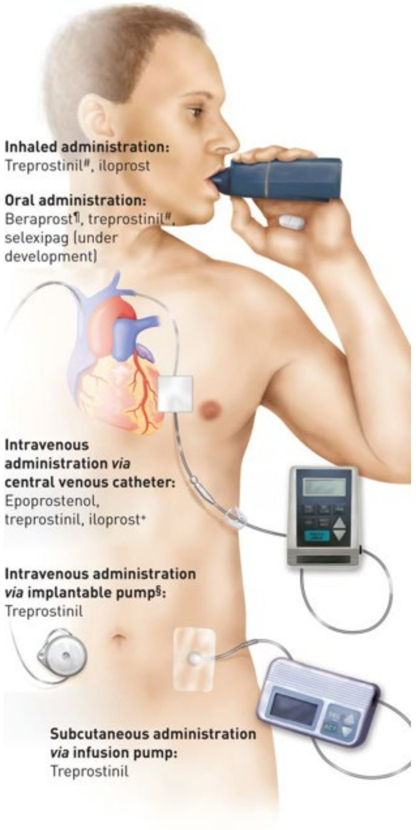


Image from 2015 publication[2]

Route	Key Benefit…	…But known issues	Notes
Oral	**+ Convenient**	**– Systemic toxicities** **– Minimal symptom relief**	• Increases side effects in GI, nervous, and vascular systems, making up-titration challenging[1,2] • Requires up-titration which is challenging given side effects[2]
Infused	**+ Effective**	**– Systemic toxicities** **– Site pain** **– Lifestyle limitations** **– Infection risk[1-3]**	• Up to 63% of PAH patients describe side effects as impairing therapeutic function[6]
Nebulized	**+ Targeted**	**– Many breaths to achieve therapeutic doses**	• Limits max dose due to throat irritation and adverse events[3] • Requires water, power, supplies, cleaning, time to administer[4]
NET IMPACT	**Many patients never experience the benefit of prostacyclin analogs** • Only 34% of patients enrolled in the REVEAL registry received a Prostacyclin analog[7] • Only 56% of patients with a PAH-related death were treated with parenteral prostacyclin before death (30% were not receiving any prostacyclin therapy)[8]		

GI, gastrointestinal; IV, intravenous.

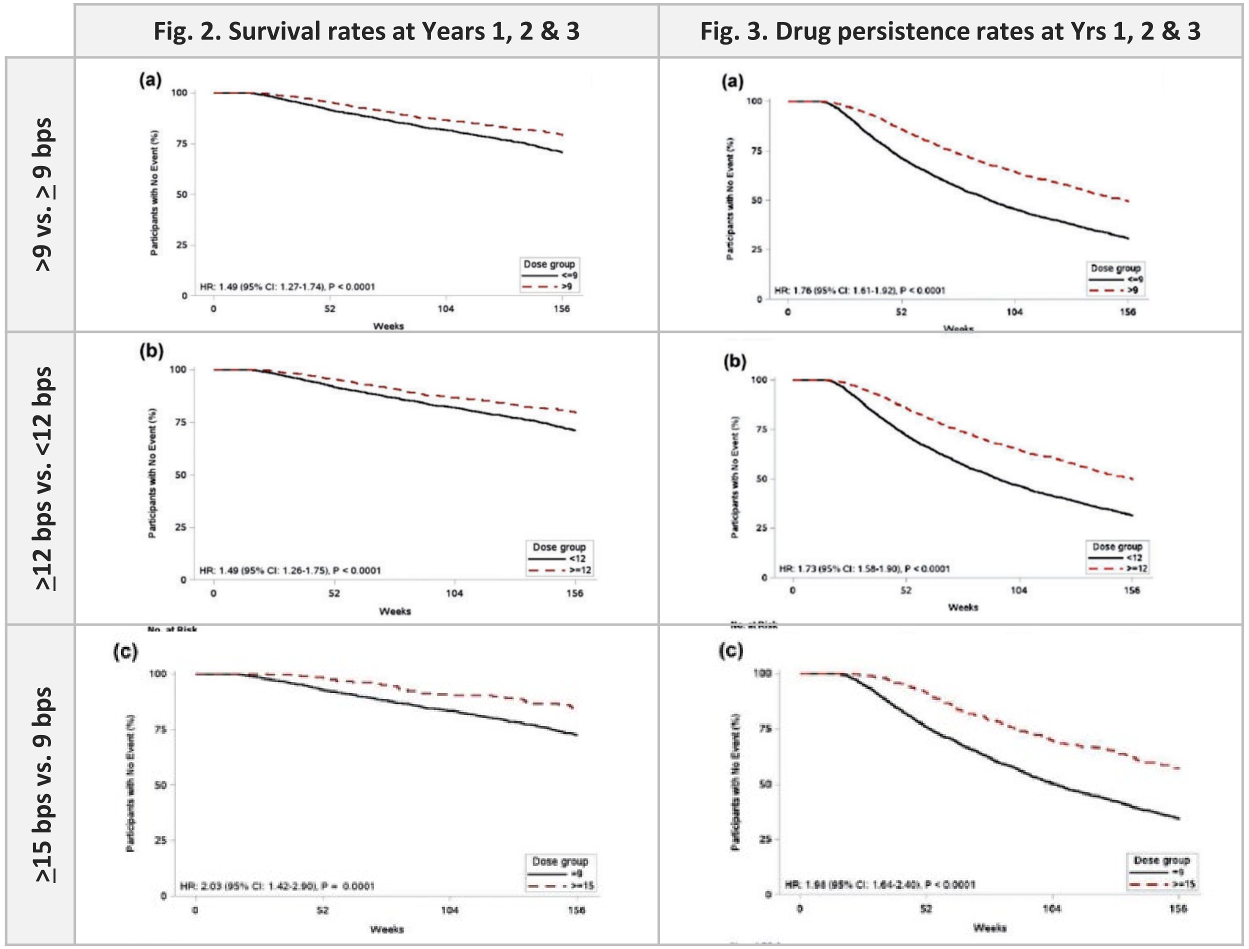
1. Garcia A, et. al. *J Drug Deliv*. 2012;2012:941243. 2. Coons JC, et al. *Pulm Circ*. 2016 Mar;6(1):132-135. 3. Lang IM, Gaine SP. *Eur Respir Rev*. 2015;24(138):630-641. 4. Hill NS, et al. INSPIRE: A Phase 3, Open-Label, Multicenter Study to Evaluate the Safety and Tolerability of LIQ861 in Pulmonary Arterial Hypertension (PAH) (Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil NCT03399604). Poster presented at: The American Thoracic Society (ATS) Conference 2019; May 21, 2019; Dallas, TX. 5. Klinger JR, et al. Chest. 2019 Mar;155(3):565-586. 6. Burger CD, et al. Psychosocial and Financial Burden of Medical Treatment in Pulmonary Artery Hypertension. Poster presented via: Pulmonary Vascular Research Institute, February 15, 2020. 7.Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010;137(2):376-387. doi:10.1378/chest.09-1140 8.Farber HW, Miller DP, Meltzer LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. J Heart Lung Transplant. 2013;32(11):1114-1122. doi:10.1016/j.healun.2013.08.010

Higher Doses of Inhaled Treprostinil Resulted in Improved Disease Control

Retrospective study of 5,000 patients from specialty pharmacy records

Higher dosed patients (>9 breaths)…

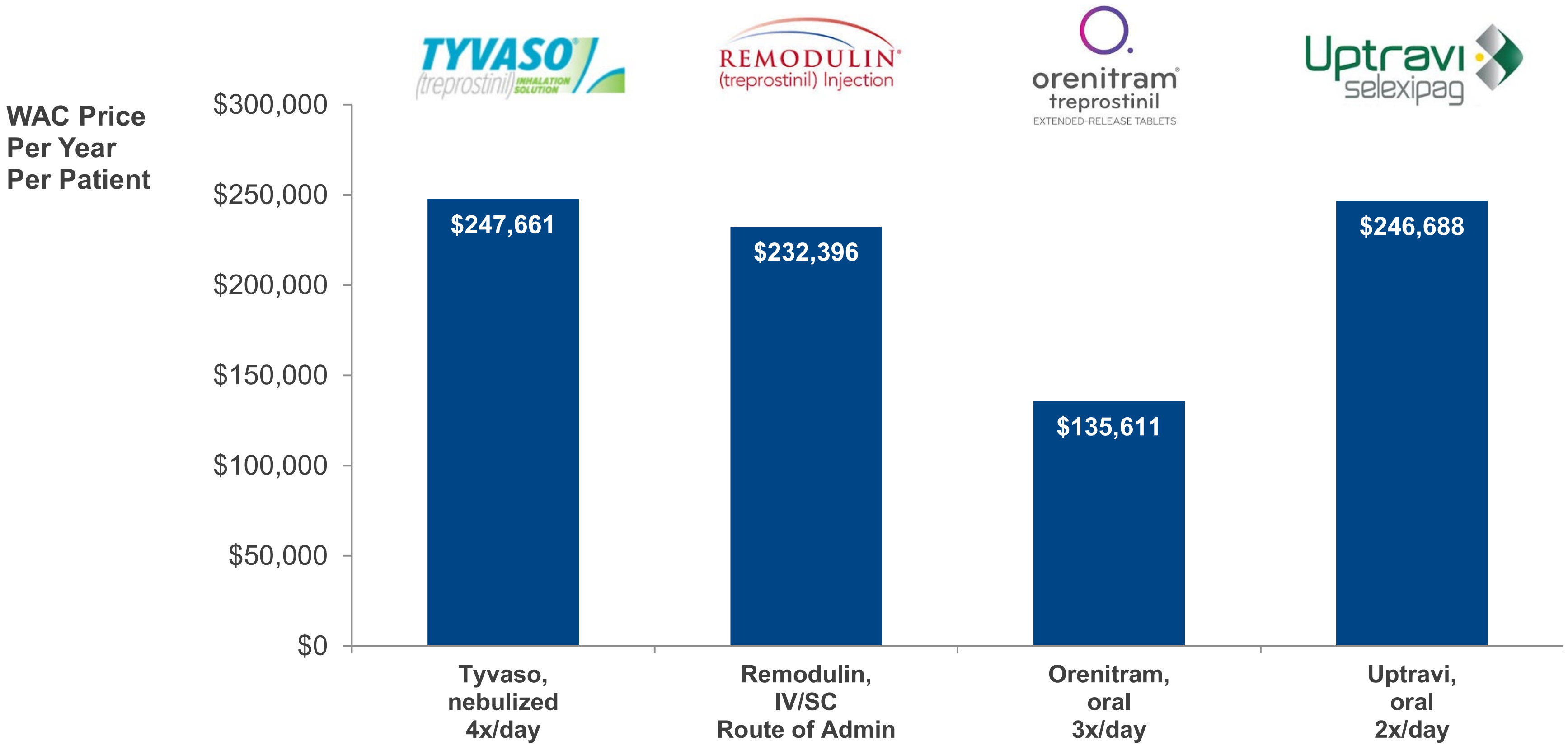
- **Improved survival rates** were seen in each time period analyzed (yrs. 1 thru 3)
- **Longer time to transition to parenteral therapy** (17.5 months vs 9.5 months)
- **Greater drug persistence** was seen in each time period analyzed (yrs. 1 thru 3)



Shapiro S, Mandras S, Restrepo-Jaramillo R, et al. Survival and drug persistence in patients receiving inhaled treprostinil at doses greater than 54 µg (nine breaths) four times daily. *Pulm Circ.* 2021;11(4):20458940211052228. Published 2021 Oct 29.

Tyvaso WAC Price Within the Branded Prostanoid Class Supports Market Value

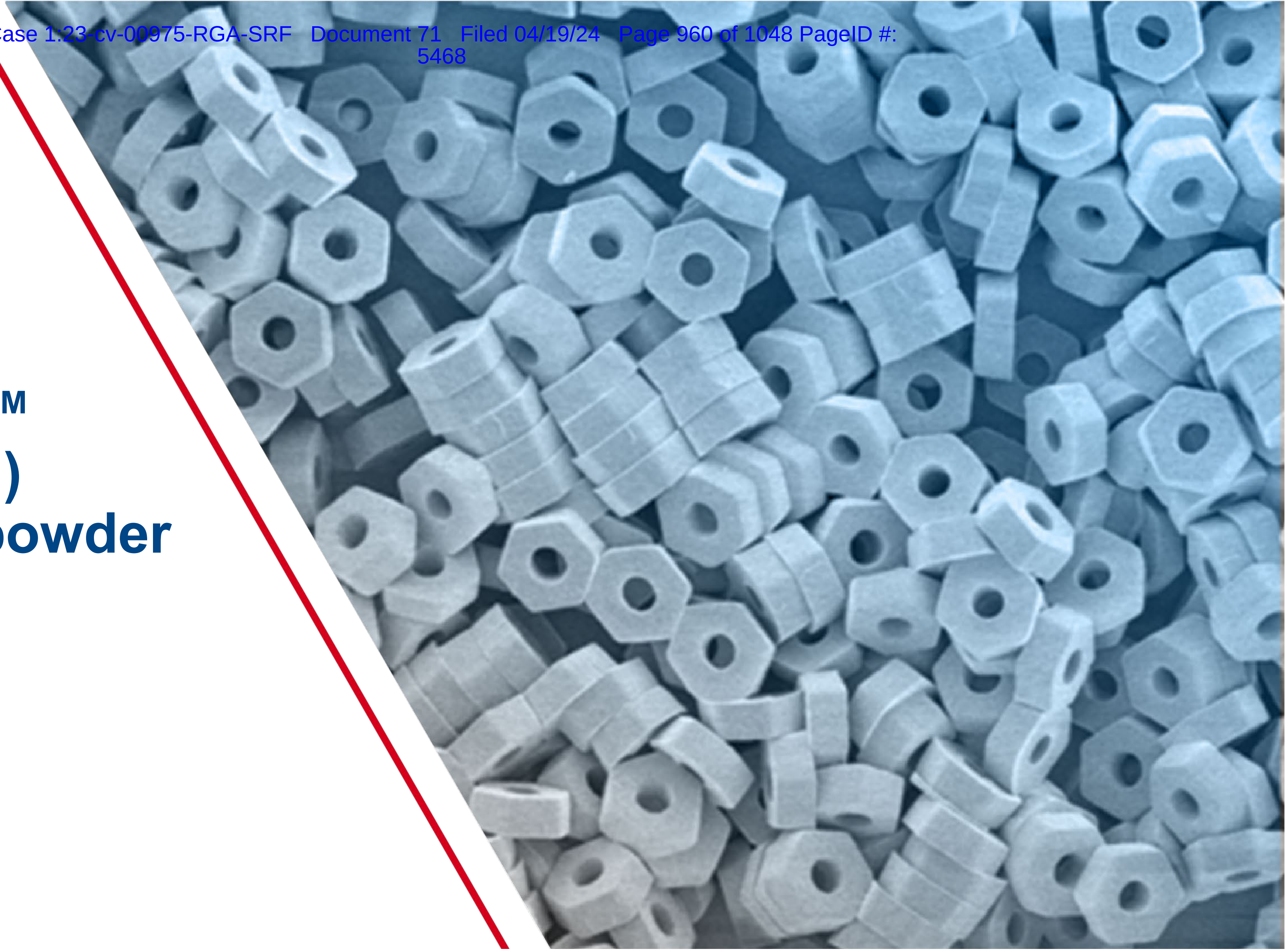
Wholesale Acquisition Cost Per Year in 2022



Source: Medi-Span April 2022; the annual WAC price is calculated by dividing the package SKU into a price per day multiplied by 365 days per year. Ventavis price is shown at 6 doses per day, lower end of range of 6-9 times/day, Tyvaso price is derived from its 28-day package quantity price, Remodulin price is shown at a dose of 10 mgs per day, Orenitram price is shown at a dose of 2.5 mg TID, Uptravi price is shown for doses ranging from 400 – 1600 mcg BID

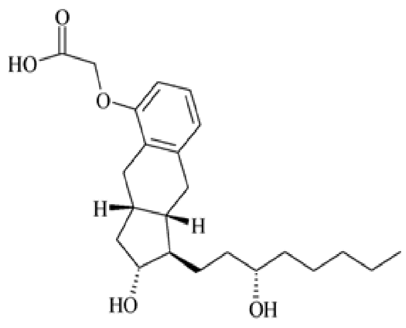
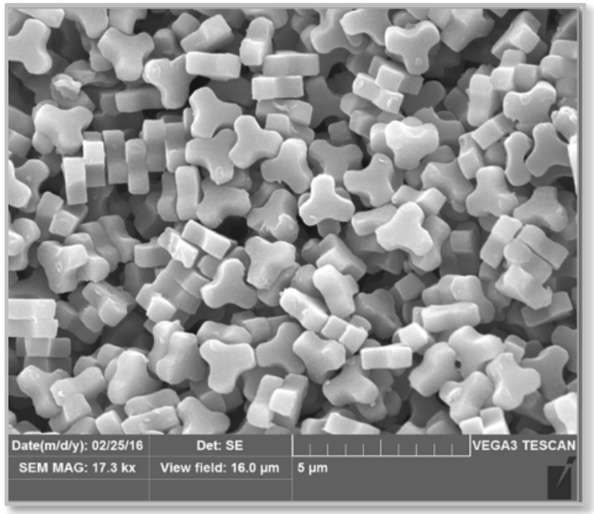
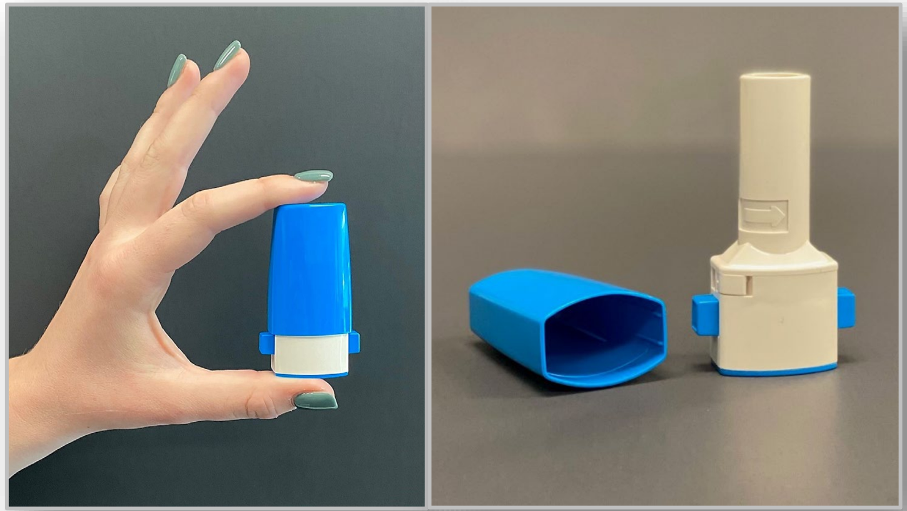
YUTREPIA™ (treprostinil) inhalation powder

Clinical Overview



YUTREPIA™ Leverages PRINT to Enhance Deep Lung Deposition

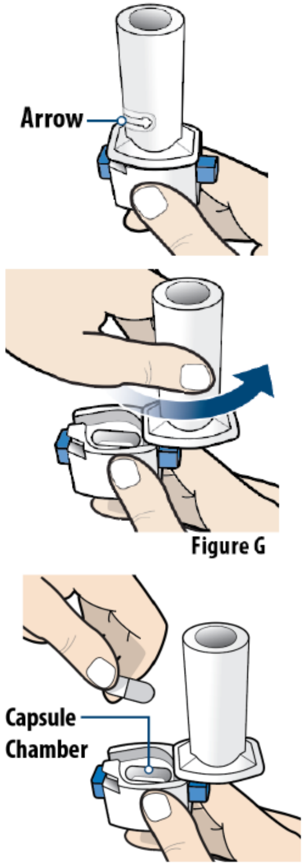
Each particle has a uniform size and shape[1]

Treprostinil	YUTREPIA Dry-Powder Formulation	Dry-Powder Inhaler
		
Treprostinil (prostacyclin analog)	**Particles are 1.3 µm in size with trefoil shape**	**Compact, disposable inhaler previously approved by FDA and EMEA**

1.Liquidia Data on File.

Inhaled Device Design Trusted for Decades Across Diseases

Plastiape sells millions of units globally of the RS00 & RS01 devices to deliver generic and branded drugs



Examples of Plastiape devices (not exhaustive)			
Company	*Program (Stage)*	*Disease*	
NOVARTIS	**Foradil®** *FDA Approved* *2001*	**COPD & Asthma**	
Chiesi	**Bronchitol®** *FDA Approved* *2020*	**Cystic Fibrosis**	
insmed	**TPIP, pro-drug** *Phase 2a & 2b* *2022*	**PAH & PH-ILD**	
gossamerbio	**GB-002, seralutinib** *Phase 2b* *2022*	**PAH & PH-ILD**	

https://bronchitol.com/hcp/dosing-and-administration/; https://investor.insmed.com/index; https://ir.gossamerbio.com;

Well-Tolerated in Phase 1 Studies with Dose Proportional Pharmacokinetics

Observed dose proportionality & no MTD[1]

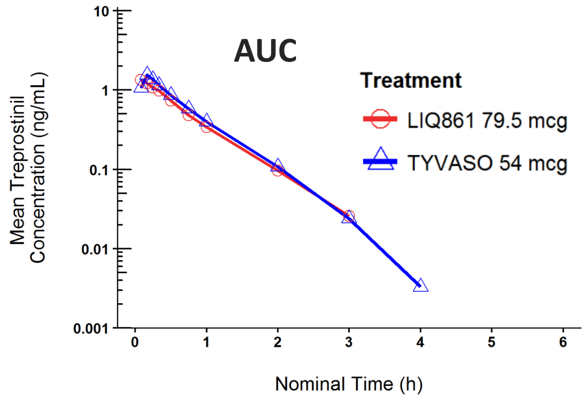
- Conducted multiple Phase 1 studies in healthy volunteers to establish safety and PK
- All Treatment Emergent Adverse Events (TEAEs) were expected based on the known safety profile of inhaled treprostinil
- Most commonly reported were cough and nausea
- No Serious Adverse Events (SAEs)
- No observed Maximum Tolerated Dose (MTD)
- Treprostinil exposure was dose proportional across 5 doses administered

Established comparable PK to Tyvaso (9 breaths)[2]

Table 3. Summary of statistical assessment of comparative bioavailability results

Agent	Parameter	GMR	90% CI	Within Subject % CV
LIQ861 79.5 µg vs Tyvaso® 54 µg	AUC_{inf}	0.923	0.802, 1.064	14.6
LIQ861 79.5 µg vs Tyvaso® 54 µg	AUC_{last}	0.947	0.812, 1.103	15.8
LIQ861 79.5 µg vs Tyvaso® 54 µg	C_{max}	0.931	0.819, 1.059	13.3

CI, confidence interval; CV, coefficient of variation; GMR, geometric least-squares mean ratio.



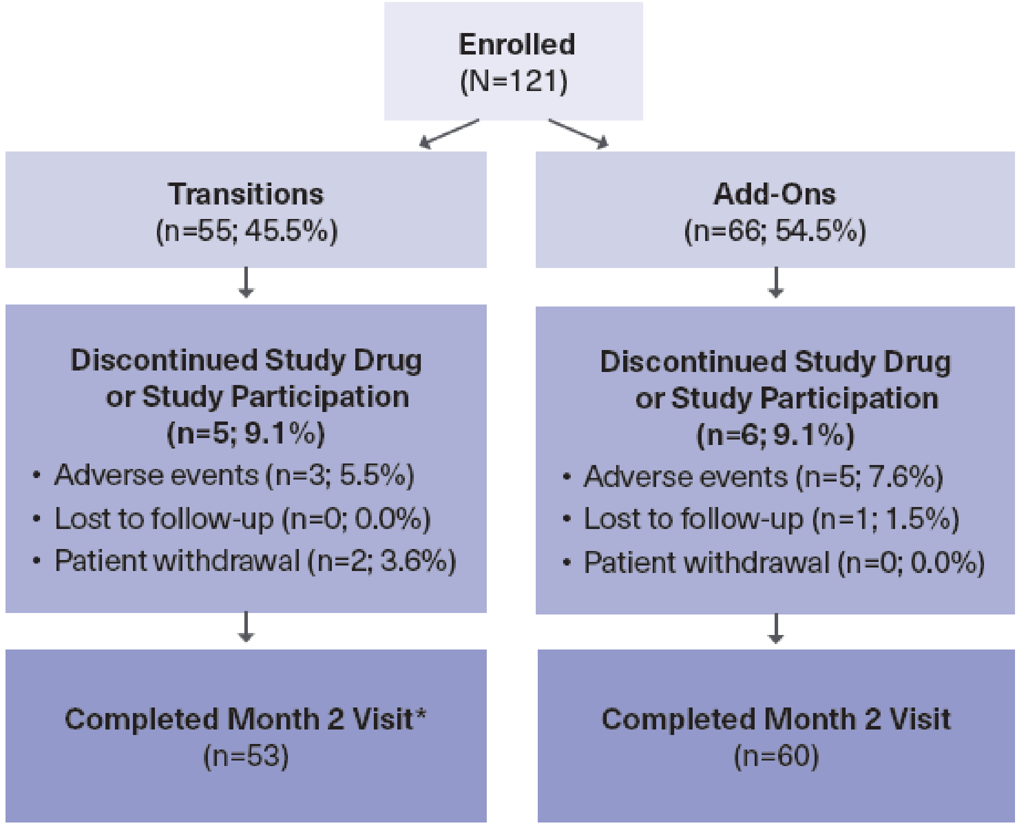
"…the **90% CIs for these ratios were within the acceptable equivalence limits of 0.80 to 1.25** (Table 3)."

1. Royal M, et al. Preclinical and Phase 1 Clinical Characterization of LIQ861, a New Dry Powder Formulation of Treprostinil [poster]. PVRI Annual World Congress 2018
2. Roscigno R, et al. Pharmacokinetic (PK) performance of LIQ861 and evaluation of comparative bioavailability with Tyvaso® in healthy subjects (Study LTI-102) [poster]. 14th PVRI Annual World Congress on Pulmonary Vascular Disease 2020

INSPIRE Study was Informed by FDA and 505(b)(2) Regulatory Pathway

Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil

Design	• Open-label, U.S. multicenter
Population	• At least 100 WHO Group I (PAH) patients • NYHA Class II, III and IV
Criteria	• **Transitions**…on stable dose of Tyvaso® for ≥3 months • **PCY Naïve (Add-Ons)**…≤2 approved non-PGI oral Rx
Primary endpoint	• **Incidence of TEAEs and SAEs at 2 months**
Exploratory endpoints	• 6 minute walk distance (6MWD) • Sustained treatment transition (Tyvaso® transitions) • NYHA functional class improvement • Quality of life using Minnesota Living with Heart Failure Questionnaire (MLHFQ)



*3 of the Transitions patients discontinued after the Month 2 timepoint.

Sources: https://clinicaltrials.gov/ct2/show/NCT03399604; PCY – prostacyclin; TEAEs – treatment-emergent adverse events; SAEs – serious adverse events

Enrollment Driven Primarily By Functional Class II & Faster Than Expected

Suggests potential interest to use as a first-line prostacyclin

		Transitions (n=55)	Prostacyclin Naïve (n=66)	Overall (n=121)
Sex	Female	47 (85.5%)	52 (78.8%)	99 (81.8%)
Age (years)	Mean ± SD	53 ± 14.1	55 ± 14.6	54 ± 14.3
BMI (kg/m^2)	Mean ± SD	30.07 ± 7.9	29.31 ± 7.8	29.66 ± 7.8
NYHA Functional Class at Screening	Class II	43 (78.2%)	37 (56.1%)	80 (66.1%)
	Class III	12 (21.8%)	29 (43.9%)	41 (33.9%)
PAH Duration (years)	Mean ± SD	7.25 ± 5.1	4.71 ± 5.1	5.87 ± 5.2
Sustained Therapy at Month 2		53 (96%)	60 (91%)	113 (93%)
*Discontinued ≤ Month 2^*		*5*	*6*	*11*

^Patients discontinued at or prior to Month 2 due to adverse events, patient choice, investigator decision, lost to follow up;
Hill N. S., et al. INSPIRE: Final Results from a Phase 3, Open-Label, Pivotal Study to Evaluate the Safety and Tolerability of LIQ861 in PAH [virtual presentation]

Established Favorable Safety Profile Across Doses Studied Without Seeing MTD

Primary endpoint at Month 2 presented at ISHLTv 2020 and Year 1 update presented at ATS 2022

TEAEs at Month 2[1] in ≥ 4% of Patients Receiving LIQ861	YUTREPIA (treprostinil) inhalation powder		
	Transitions (n=55)	**Naïve (n=66)**	**All treated (n=121)**
Cough	27.3%	54.5%	**42.1%**
Headache	25.5%	27.3%	**26.4%**
Throat irritation	9.1%	21.2%	**15.7%**
Dizziness	10.9%	10.6%	**10.7%**
Diarrhea	5.5%	12.1%	**9.1%**
Chest discomfort	9.1%	7.6%	**8.3%**
Nausea	7.3%	7.6%	**7.4%**
Flushing	1.8%	7.6%	**5.0%**
Dyspnea	5.5%	4.5%	**5.0%**
Oropharyngeal pain	1.8%	6.1%	**4.1%**

- **No SAEs related to study drug**
- **TEAEs mostly mild to moderate & during first 2 weeks**
- **Titrated most patients ≥ 79.5 mcg doses by Month 2**
- **Dosed up to 159 mcg at Month 2 in INSPIRE study**
- **Dosed up to 238.5 mcg in Extension study**
- **Have not yet reached an MTD**
- **No important adverse safety outcomes at Year 1**[2]

Serious Adverse Events (SAEs); Treatment Emergent Adverse Events (TEAEs) deemed related to LIQ861; Maximum Tolerated Dose (MTD);

1. Hill et al, ISHLTv 2020 [virtual presentation]. 2. Hill et al, ATS 2022 [Symposium, Poster]

Positive Trends in Exploratory Endpoint Data at Month 2 Primary Endpoint

Exploratory endpoints from INSPIRE study, not controlled, open-label

Maintained or improved NYHA Functional Class at Month 2[1]

98% for Transition pts
95% for Naïve pts

Increased Median 6MWD at Month 2[1]

+ 18.9m for Transition pts
+ 6.5m for Naïve pts

Significant improvement in quality of life as measured by MLHFQ[2,3]

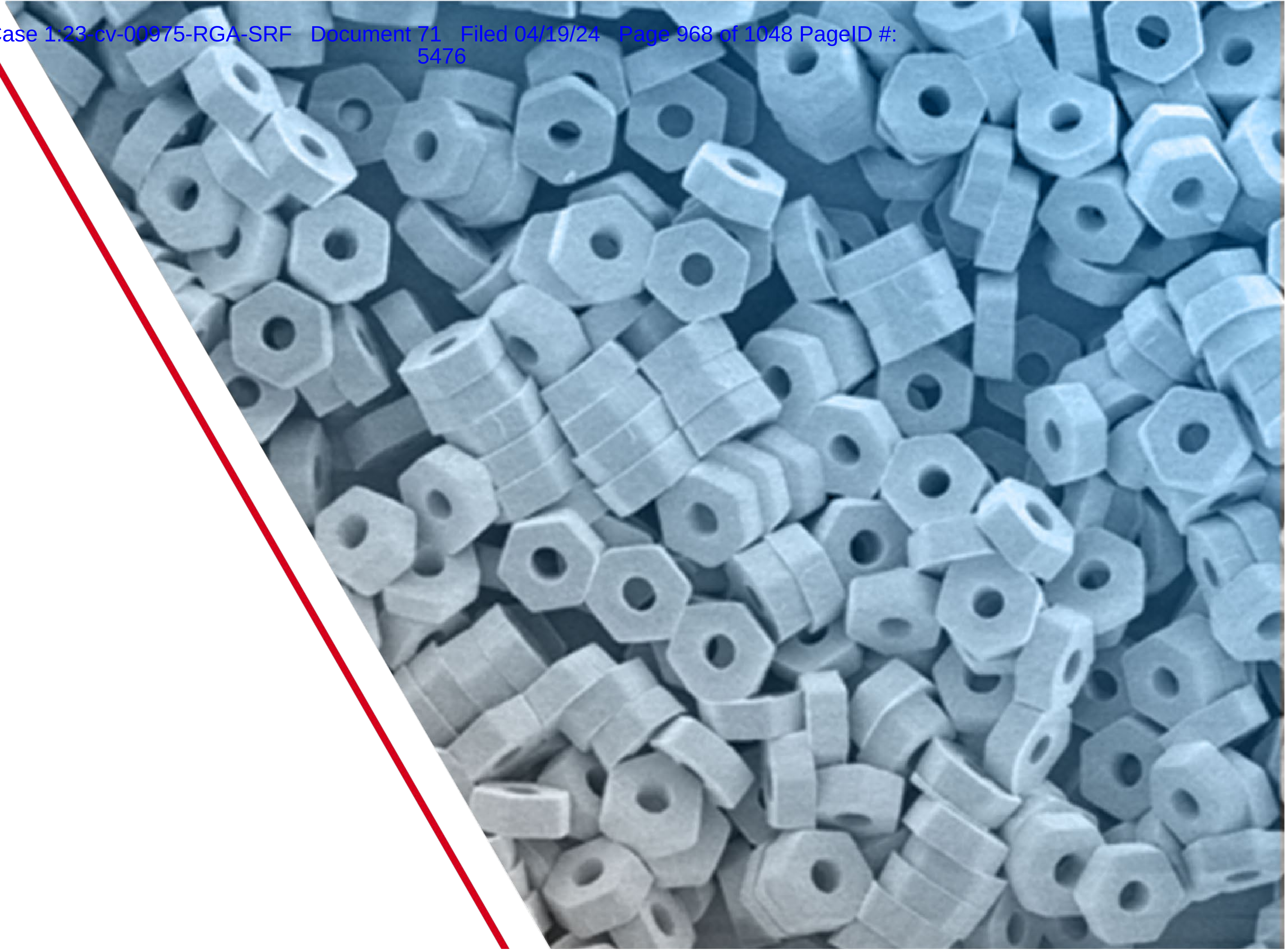
Emotional and Physical Dimensions scored

- **Greater percentage of subjects met 2 or 3 PAH low-risk criteria**
- **Did not observe clinically meaningful change in NT-proBNP**
- **Majority of transition patients preferred dry powder inhaler to Tyvaso® Inhalation System**

New York Heart Association (NYHA); Six Minute Walk Distance (6MWD); Minnesota Living with Heart Failure Questionnaire (MLHFQ); N-terminal pro b-type natriuretic peptide (NT-proBNP)

1. Hill et al, ATS 2020 [ePoster]; 2. Hill et al, ATS 2020 [Poster] 3. Kingman et al; PHA 2022 [Poster] Tyvaso® is a registered trademark of United Therapeutics

Legal & Financial Positioning



Legal Events are Gating to Final FDA Approval of YUTREPIA™

	Q1 2022	Q2 2022		Q3 2022		Q4 2022
Key Dates	Hatch-Waxman Trial △ Mar 28-31	'793 IPR oral arguments △ May-13	Submit H-W Post-trial briefs △ Jun-15	'793 IPR Written Decision △ by Aug-11	Hatch-Waxman Decision △	30-Mo Stay Expires ▲ Oct-27

U.S. Patents Asserted by UTHR	Legal Proceeding	Next Step	Comments
'901	Hatch-Waxman Litigation[1,2]	✓ Withdrawn	• PTAB stated 7 of 9 claims unpatentable in IPR decision (Oct 2021)[3] • UTHR stipulated LQDA's non-infringement with appellate rights reserved (Dec 2021)[4] • PTAB denied UTHR's request for re-hearing on IPR (June 2022)
'066		Await H-W Decision	• Product-by-process claims relate to product that is similar to product claimed in related patent invalidated by IPR[5] • Process claim requires actual storage at ambient temperature
'793	H-W Litigation	Await H-W Decision	• '793 IPR instituted 1 year after patent was granted (Aug 2021)[6] • PTAB stated reasonable likelihood that at least one challenged claim is unpatentable • Conducted IPR oral arguments on May-13; written decision expected near Aug-11
	Inter Partes Review	Await Written Decision	

- **U.S. Patent numbers**: Patent 9,604,**901**, Patents 9,593,**066,** Patent 10,716,**793**
- **Under Hatch-Waxman Act:** FDA is automatically precluded from granting final approval of YUTREPIA for up to 30 months or earlier favorable resolution of lawsuit filed by UTHR in Jun-2020

Patent Trial And review Board (PTAB); *Inter Partes* Review (IPR); Press releases: 1. Jun 2020; 2. Jul 2020; 3. Oct 2021; 4. Dec 2021 5. Nov 2017 (SteadyMed); 6. Aug 2021
PACER: Civil Docket For Case#: 1:20-cv-00755-RGA-JLH on https://ecf.ded.uscourts.gov/; PTAB: IPR2021-00406 on https://ptab.uspto.gov/#/external/search

Well Capitalized Through Potential Value Creating Events In 2022

- **Positive contribution from Treprostinil Injection**
  - 50:50 profit split with Sandoz
  - $15.5 million cash contribution 2021 EOY
  - $12.9 million revenue 2021 EOY, net of $2.7 in amortization of contract acquisition costs from Sandoz agreement
  - $3.5 million revenue for 1Q'2022
- **Preparing to launch YUTREPIA™ into PAH market**
  - Pre-commercial activity with key stakeholders
  - R&D activity to increase future value proposition
  - Early-stage program for life-cycle management

Cash & Equivalents 2022 Q1	**$57.8 million** as of 31-Mar-2022
SVB Debt Facility January 2022	$20.0 million drawn +$5.0 million available now +$15.0 million on future milestones
Equity Raise April 2022	~$53.7 million in net proceeds
Shares Outstanding	64.4 million shares

Liquidia® CORPORATION

Thank You

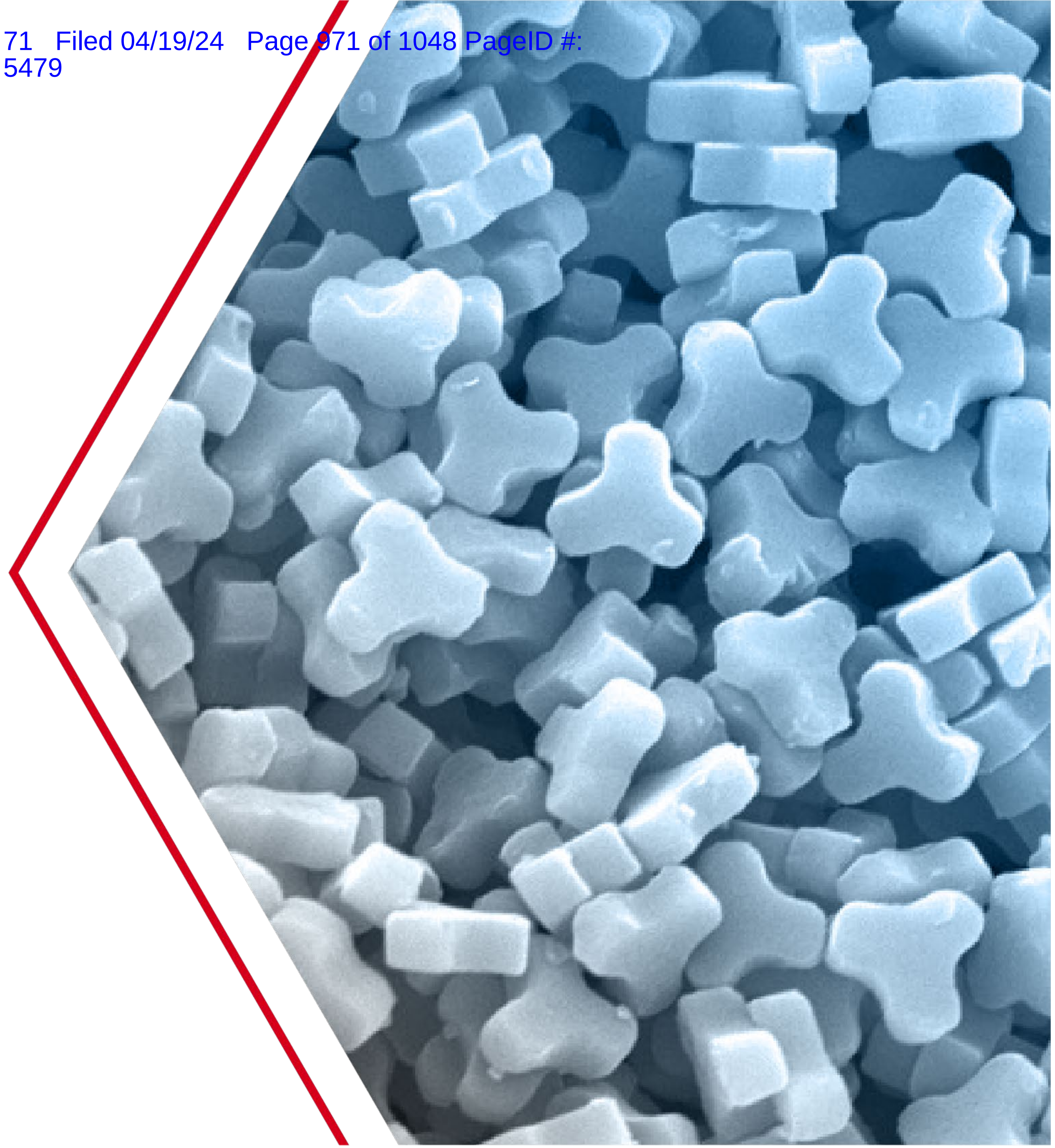


EXHIBIT 33

PRESS RELEASE

UNITED THERAPEUTICS CORPORATION REPORTS FOURTH QUARTER AND FULL YEAR 2023 FINANCIAL RESULTS

SILVER SPRING, Md. & RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)-- United Therapeutics Corporation (Nasdaq: UTHR), a public benefit corporation, today announced its financial results for the quarter and year ended December 31, 2023. Full year 2023 revenues rose to a record $2.33 billion, reflecting 20% growth over 2022.

“Congratulations to the dedicated Unitherians who worked tirelessly to help us achieve our third straight quarter and second straight year of record revenue,” said Martine Rothblatt, Ph.D., Chairperson and Chief Executive Officer of United Therapeutics. “This represents only the beginning of our growth, driven by a strong foundation in our current commercial business and upcoming enrollment milestones for our innovative pipeline. On top of this, we have continued momentum for our revolutionary organ manufacturing programs, with the first human clinical study of a bioengineered organ, the miroliver*ELAP*, cleared by the FDA, and the recent opening of the world’s first designated pathogen-free clinical supply facility to support our upcoming xenotransplantation clinical program.”

“Our commercial business remains a solid foundation supporting our innovative and revolutionary efforts to cure end stage organ disease,” said Michael Benkowitz, President and Chief Operating Officer of United Therapeutics. “To that end, in the fourth quarter we saw record revenue for our Tyvaso business, and we achieved solid growth in our U.S. Remodulin business, with strong revenue growth and a record number of patients on therapy despite the presence of generic competition since 2019.”

Fourth Quarter and Full Year 2023 Financial Results

Key financial highlights include (in millions, except per share data):

	Three Months Ended December 31,		Year Ended December 31,	
	2023	2022	2023	2022
Total revenues	$ 614.7	$ 491.5	$ 2,327.5	$ 1,936.3
Net income	$ 217.1	$ 132.1	$ 984.8	$ 727.3
Net income, per basic share	$ 4.62	$ 2.88	$ 21.04	$ 15.98
Net income, per diluted share	$ 4.36	$ 2.67	$ 19.81	$ 15.00

Revenues

The table below presents the components of total revenues (dollars in millions):

	Three Months Ended December 31,		Dollar Change	Percentage Change	Year Ended December 31,		Dollar Change	Percentage Change
	2023	2022			2023	2022		
Net product sales:								
Tyvaso DPI®(1)	$213.7	$ 92.2	$ 121.5	132%	$ 731.1	$ 158.3	$ 572.8	362%
Nebulized Tyvaso®(1)	136.9	150.1	(13.2)	(9)%	502.6	714.7	(212.1)	(30)%
Total Tyvaso	**350.6**	**242.3**	**108.3**	**45%**	**1,233.7**	**873.0**	**360.7**	**41%**
Remodulin®(2)	115.1	122.5	(7.4)	(6)%	494.8	500.2	(5.4)	(1)%
Orenitram®	84.1	75.8	8.3	11%	359.4	325.1	34.3	11%
Unituxin®	54.2	36.7	17.5	48%	198.9	182.9	16.0	9%
Adcirca®	6.8	10.4	(3.6)	(35)%	28.9	41.3	(12.4)	(30)%
Other	3.9	3.8	0.1	3%	11.8	13.8	(2.0)	(14)%
Total revenues	$614.7	$491.5	$ 123.2	25%	$2,327.5	$1,936.3	$ 391.2	20%

(1) Net product sales include both the drug product and the respective inhalation device.
(2) Net product sales include sales of infusion devices including the Remunity® Pump.

Fourth Quarter 2023 Compared to Fourth Quarter 2022. Total Tyvaso revenues grew by 45% to $350.6 million in the fourth quarter of 2023, compared to $242.3 million in the fourth quarter of 2022. This growth was primarily due to an increase in quantities sold, driven by the commercial launch of Tyvaso DPI in June 2022 and continued growth in utilization by patients with pulmonary hypertension associated with interstitial lung disease (**PH-ILD**). The growth in Tyvaso DPI revenues resulted primarily from an increase in quantities sold. The decrease in nebulized Tyvaso revenues was primarily due to a decrease in U.S. quantities sold following the commercial launch of Tyvaso DPI, partially offset by an increase in international nebulized Tyvaso revenues, primarily due to the commercial launch of nebulized Tyvaso in Japan in December 2022, as shown in the table below. The decrease in Remodulin revenues resulted from a decrease in international Remodulin revenues, partially offset by an increase in U.S. Remodulin revenues, as shown in the table below. The increase in Orenitram revenues resulted from a price increase and an increase in quantities sold. The increase in Unituxin revenues resulted from an increase in quantities sold and a price increase.

Full Year 2023 Compared to Full Year 2022. Total Tyvaso revenues grew by 41% to $1,233.7 million in 2023, compared to $873.0 million in 2022. This growth was primarily due to an increase in quantities sold, driven by the commercial launch of Tyvaso DPI in June 2022 and continued growth in utilization by patients with PH-ILD. The growth in Tyvaso DPI revenues resulted primarily from an increase in quantities sold. The decrease in nebulized Tyvaso revenues was driven by a decrease in U.S. nebulized Tyvaso revenues, primarily due to a decrease in quantities sold following the commercial launch of Tyvaso DPI, partially offset by an increase in international nebulized Tyvaso revenues, primarily due to the commercial launch of nebulized Tyvaso in Japan in December 2022, as shown in the table below. The decrease in Remodulin revenues resulted from a decrease in international Remodulin revenues, partially offset by an increase in U.S. Remodulin

United Therapeutics
CORPORATION

The table below presents the breakdown of total revenues between the United States and rest-of-world (**ROW**) (in millions):

	Three Months Ended December 31,						Year Ended December 3				
	2023			2022			2023			2	
	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	F
Net product sales:											

Tyvaso DPI[1]	$213.7	$ —	$213.7	$ 92.2	$ —	$ 92.2	$ 731.1	$ —	$ 731.1	$ 158.3	$
Nebulized Tyvaso[1]	123.7	13.2	136.9	148.4	1.7	150.1	477.1	25.5	502.6	708.6
Total Tyvaso	**337.4**	**13.2**	**350.6**	**240.6**	**1.7**	**242.3**	**1,208.2**	**25.5**	**1,233.7**	**866.9**
Remodulin[2]	106.3	8.8	115.1	97.7	24.8	122.5	414.6	80.2	494.8	407.5
Orenitram	84.1	—	84.1	75.8	—	75.8	359.4	—	359.4	325.1
Unituxin	48.7	5.5	54.2	36.4	0.3	36.7	181.3	17.6	198.9	170.5
Adcirca	6.8	—	6.8	10.4	—	10.4	28.9	—	28.9	41.3
Other	2.6	1.3	3.9	2.8	1.0	3.8	9.8	2.0	11.8	2.8
Total revenues	$585.9	$28.8	$614.7	$463.7	$27.8	$491.5	$2,202.2	$125.3	$2,327.5	$1,814.1	$

(1) Net product sales include both the drug product and the respective inhalation device.
(2) Net product sales include sales of infusion devices including the Remunity Pump.

Expenses

Cost of sales. The table below summarizes cost of sales by major category (dollars in millions):

Category:	Three Months Ended December 31, 2023	Three Months Ended December 31, 2022	Dollar Change	Percentage Change	Year Ended December 31, 2023	Year Ended December 31, 2022	Dollar Change	Percentage Change
Cost of sales	$ 70.1	$ 55.9	$ 14.2	25%	$255.1	$146.7	$ 108.4	74%
Share-based compensation expense[1]	0.9	2.9	(2.0)	(69)%	2.4	4.9	(2.5)	(51)%
Total cost of sales	$ 71.0	$ 58.8	$ 12.2	21%	$257.5	$151.6	$ 105.9	70%

(1) See *Share-based compensation* below.

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*Cost of sales, excluding share-based compensation.*The increase in cost of sales for the quarter ended December 31, 2023, as compared to the same period in 2022, was primarily due to an increase in Tyvaso DPI royalty expense and product costs following its commercial launch in June 2022.

The increase in cost of sales for the year ended December 31, 2023, as compared to the same period in 2022, was primarily due to an increase in Tyvaso DPI royalty expense and product costs, following its commercial launch in June 2022, and an increase in Remunity product sales.

Research and development expense. The table below summarizes the nature of research and development expense by major expense category (dollars in millions):

	Three Months Ended December 31,		Dollar Change	Percentage Change	Year Ended December 31,		Dollar Change	Percentage Change
	2023	2022			2023	2022		
Category:								
External research and development[1]	$ 50.4	$ 46.7	$ 3.7	8%	$192.0	$168.8	$ 23.2	14%
Internal research and development[2]	43.2	35.4	7.8	22%	146.6	131.4	15.2	12%
Share-based compensation expense[3]	5.7	11.0	(5.3)	(48)%	15.6	23.8	(8.2)	(34)%
Impairments[4]	—	—	—	—%	—	—	—	—%
Other[5]	52.1	0.8	51.3	NM[6]	53.8	(1.1)	54.9	NM[6]
Total research and development expense	$151.4	$ 93.9	$ 57.5	61%	$408.0	$322.9	$ 85.1	26%

(1) *External research and development* primarily includes fees paid to third parties (such as clinical trial sites, contract research organizations, and contract laboratories) for preclinical and clinical studies and payments to third-party contract manufacturers before FDA approval of the relevant product.

(2) *Internal research and development* primarily includes salary-related expenses for research and development functions, internal costs to manufacture product candidates before FDA approval, and internal facilities-related expenses, including depreciation, related to research and development activities.

(3) See *Share-based compensation*below.

(4) *Impairments* primarily includes impairment charges to write down the carrying value of in-process research and development (IPR&D) and of certain property, plant, and equipment as a result of research and development activities. There were no impairment charges during the years ended December 31, 2023 and December 31, 2022.

(5) *Other* primarily includes upfront fees and milestone payments to third parties under license agreements related to development-stage products, adjustments to the fair value of our contingent consideration obligations, and costs to acquire certain IPR&D assets. During the quarter and year ended December 31, 2023, we recorded $46.0 million in IPR&D expense in connection with the acquisition of IVIVA Medical, Inc. (IVIVA).

(6) Calculation is not meaningful.

Research and development, excluding share-based compensation. The increase in research and development expense for the quarter ended December 31, 2023, as compared to the same period in 2022, was due to an increase in IPR&D expense in connection with the acquisition of IVIVA and increased expenditures related to the *TETON 1* and *TETON 2* clinical studies of nebulized Tyvaso in patients with idiopathic pulmonary fibrosis (IPF).

The increase in research and development expense for the year ended December 31, 2023, as compared to the same period in 2022, was due to: (1) an increase in IPR&D expense in connection with the acquisition of IVIVA; (2) increased expenditures related to the *TETON 1* and *TETON 2* clinical studies of nebulized Tyvaso in patients with IPF; and (3) increased expenditures related to organ manufacturing projects.

Selling, general, and administrative expense. The table below summarizes selling, general, and administrative expense by major category (dollars in millions):

	Three Months Ended December 31,		Dollar Change	Percentage Change	Year Ended December 31,		Dollar Change	Percentage Change
	2023	2022			2023	2022		
Category:								

General and administrative	$ 98.1	$ 89.3	$ 8.8	10%	$374.2	$333.2	$ 41.0	12%
Sales and marketing	24.1	23.0	1.1	5%	81.8	70.8	11.0	16%
Share-based compensation expense(1)	10.0	50.9	(40.9)	(80)%	21.1	78.1	(57.0)	(73)%
Total selling, general, and administrative expense	$132.2	$163.2	$ (31.0)	(19)%	$477.1	$482.1	$ (5.0)	(1)%

(1) See *Share-based compensation* below.

General and administrative, excluding share-based compensation. The increase in general and administrative expense for the year ended December 31, 2023, as compared to the same period in 2022, was primarily due to increases in: (1) office expenses; (2) personnel expense due to growth in headcount; and (3) sponsorships and grants.

Sales and marketing, excluding share-based compensation. The increase in sales and marketing expense for the year ended December 31, 2023, as compared to the same period in 2022, was primarily due to increases in: (1) personnel expense due to growth in headcount; and (2) consulting expenses.

Share-based compensation. The table below summarizes share-based compensation expense by major category (dollars in millions):

	Three Months Ended December 31,		Dollar Change	Percentage Change	Year Ended December 31,		Dollar Change	Percentage Change
	2023	2022			2023	2022		
Category:								
Stock options	$ 2.9	$ 5.8	$ (2.9)	(50)%	$ 15.4	$ 22.6	$ (7.2)	(32)%
Restricted stock units	14.1	12.1	2.0	17%	52.4	35.7	16.7	47%
Share tracking awards plan (STAP)	(0.9)	46.5	(47.4)	(102)%	(30.7)	46.7	(77.4)	(166)%

Employee stock purchase plan	0.5	0.4	0.1	25%	2.0	1.8	0.2	11%
Total share-based compensation expense	$ 16.6	$ 64.8	$ (48.2)	(74)%	$ 39.1	$106.8	$ (67.7)	(63)%

The decrease in share-based compensation expense for the quarter ended December 31, 2023, as compared to the same period in 2022, was primarily due to an increase in STAP benefit driven by a three percent decrease in our stock price during the quarter ended December 31, 2023, as compared to a 33 percent increase in our stock price for the same period in 2022. The decrease in share-based compensation expense for the year ended December 31, 2023, as compared to the same period in 2022, was primarily due to: (1) an increase in STAP benefit driven by a 21 percent decrease in our stock price during 2023, as compared to a 29 percent increase in our stock price during 2022; and (2) a decrease in stock option expense due to fewer awards remaining outstanding in 2023, as compared to the same period in 2022, partially offset by an increase in restricted stock unit expense.

Other expense, net. The change in other expense, net for the year ended December 31, 2023, as compared to the same period in 2022, was primarily due to net unrealized and realized gains and losses on equity securities.

Income tax expense. Income tax expense was $289.5 million for the year ended December 31, 2023, compared to $223.3 million for the same period in 2022. Our effective income tax rate was approximately 23 percent for the years ended December 31, 2023 and 2022.

Inducement Restricted Stock Units

On February 19, 2024, we granted a total of 11,250 restricted stock units under our 2019 Inducement Stock Incentive Plan to six newly hired employees. All of these restricted stock units will vest in full on February 19, 2027, the third anniversary of the grant date, assuming continued employment on such date, and subject to the standard terms and conditions we filed with the SEC as Exhibit 10.2 to our Current Report on Form 8-K on March 1, 2019. We are providing this information in accordance with Nasdaq Listing Rule 5635(c)(4).

Webcast

We will host a webcast to discuss our fourth quarter and full year 2023 financial results on Wednesday, February 21, 2024, at 9:00 a.m. Eastern Time. The webcast can be accessed live via our website at https://ir.unither.com/events-and-presentations/default.aspx. A replay of the webcast will also be available at the same location on our website.

United Therapeutics: Enabling Inspiration

At United Therapeutics, our vision and mission are one. We use our enthusiasm, creativity, and persistence to innovate for the unmet medical needs of our patients and to benefit our other stakeholders. We are bold and unconventional. We have fun, we do good. We are the first publicly-traded biotech or pharmaceutical company to take the form of a public benefit corporation (**PBC**). Our public benefit purpose is
to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs
.

You can learn more about what it means to be a PBC here: unither.com/pbc.

Forward-Looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, statements related to our future growth expectations from both our current commercial operations and our pipeline; our organ manufacturing programs, including our efforts to cure end-stage organ disease and the anticipated clinical trials of miroliver*ELAP* and our xenotransplantation program; and our goals of innovating for the unmet medical needs of our patients and to benefit our other stakeholders, furthering our public benefit purpose of developing novel pharmaceutical therapies and technologies that expand the availability of transplantable organs. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of February 21, 2024, and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events, or any other reason.

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ADCIRCA is a registered trademark of Eli Lilly and Company.

UNITED THERAPEUTICS CORPORATION
CONSOLIDATED STATEMENTS OF OPERATIONS
(In millions, except per share data)

	Three Months Ended December 31,		Year Ended December 31,	
	2023	2022	2023	2022
	(Unaudited)			
Total revenues	$ 614.7	$ 491.5	$ 2,327.5	$ 1,936.3
Operating expenses:				
Cost of sales	71.0	58.8	257.5	151.6
Research and development	151.4	93.9	408.0	322.9
Selling, general, and administrative	132.2	163.2	477.1	482.1
Total operating expenses	354.6	315.9	1,142.6	956.6
Operating income	260.1	175.6	1,184.9	979.7
Interest income	51.0	20.8	162.7	45.2
Interest expense	(15.1)	(12.3)	(59.3)	(32.4)
Other expense, net	(0.6)	(5.3)	(14.0)	(40.2)
Impairment of investment in privately-held company	—	—	—	(1.7)
Total other income (expense), net	35.3	3.2	89.4	(29.1)
Income before income taxes	295.4	178.8	1,274.3	950.6
Income tax expense	(78.3)	(46.7)	(289.5)	(223.3)
Net income	$ 217.1	$ 132.1	$ 984.8	$ 727.3
Net income per common share:				
Basic	$ 4.62	$ 2.88	$ 21.04	$ 15.98
Diluted	$ 4.36	$ 2.67	$ 19.81	$ 15.00
Weighted average number of common shares outstanding:				
Basic	47.0	45.8	46.8	45.5
Diluted	49.8	49.4	49.7	48.5

SELECTED CONSOLIDATED BALANCE SHEET DATA
(In millions)

	December 31, 2023	December 31, 2022
Cash, cash equivalents, and marketable investments	$ 4,903.9	$ 4,154.9
Total assets	7,167.0	6,044.5
Total liabilities	1,182.2	1,247.8
Total stockholders' equity	5,984.8	4,796.7

The table below presents the breakdown of select historical total revenues between the United States and ROW (in millions):

	Three Months Ended										
	March 31, 2023			June 30, 2023			September 30, 2023			Decemb	
	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	R
Net product sales:											
Tyvaso DPI(1)	$118.7	$ —	$118.7	$193.6	$ —	$193.6	$205.1	$ —	$205.1	$213.7	$
Nebulized Tyvaso(1)	115.7	4.0	119.7	119.6	5.7	125.3	118.1	2.6	120.7	123.7	
Total Tyvaso	**234.4**	**4.0**	**238.4**	**313.2**	**5.7**	**318.9**	**323.2**	**2.6**	**325.8**	**337.4**	
Remodulin(2)	93.2	28.2	121.4	103.5	23.7	127.2	111.6	19.5	131.1	106.3	
Orenitram	88.2	—	88.2	95.1	—	95.1	92.0	—	92.0	84.1	
Unituxin	44.3	4.8	49.1	39.5	4.8	44.3	48.8	2.5	51.3	48.7	
Adcirca	7.3	—	7.3	7.5	—	7.5	7.3	—	7.3	6.8	
Other	2.3	0.2	2.5	3.2	0.3	3.5	1.7	0.2	1.9	2.6	
Total revenues	$469.7	$37.2	$506.9	$562.0	$34.5	$596.5	$584.6	$24.8	$609.4	$585.9	$

	Three Months Ended										
	March 31, 2022			June 30, 2022			September 30, 2022			Decemb	
	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	R
Net product sales:											

Tyvaso DPI(1)	$ —	$ —	$ —	$ 3.0	$ —	$ 3.0	$ 63.1	$ —	$ 63.1	$ 92.2	$
Nebulized Tyvaso(1)	170.1	1.9	172.0	196.2	1.8	198.0	193.9	0.7	194.6	148.4	
Total Tyvaso	**170.1**	**1.9**	**172.0**	**199.2**	**1.8**	**201.0**	**257.0**	**0.7**	**257.7**	**240.6**	
Remodulin(2)	99.1	32.6	131.7	108.5	23.5	132.0	102.2	11.8	114.0	97.7	
Orenitram	82.8	—	82.8	79.0	—	79.0	87.5	—	87.5	75.8	
Unituxin	48.0	7.6	55.6	43.3	1.2	44.5	42.8	3.3	46.1	36.4	
Adcirca	9.8	—	9.8	10.4	—	10.4	10.7	—	10.7	10.4	
Other	—	10.0	10.0	—	—	—	—	—	—	2.8	
Total revenues	$409.8	$52.1	$461.9	$440.4	$26.5	$466.9	$500.2	$15.8	$516.0	$463.7	$

	Three Months Ended										
	March 31, 2021			June 30, 2021			September 30, 2021			Decemb	
	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	ROW	Total	U.S.	R
Net product sales:											
Tyvaso DPI(1)	$ —	$ —	$ —	$ —	$ —	$ —	$ —	$ —	$ —	$ —	$
Nebulized Tyvaso(1)	122.4	0.6	123.0	152.6	1.2	153.8	160.7	3.5	164.2	165.0	
Total Tyvaso	**122.4**	**0.6**	**123.0**	**152.6**	**1.2**	**153.8**	**160.7**	**3.5**	**164.2**	**165.0**	
Remodulin(2)	107.1	23.1	130.2	111.0	28.8	139.8	106.8	18.6	125.4	98.5	
Orenitram	72.4	—	72.4	76.2	—	76.2	85.2	—	85.2	72.3	
Unituxin	42.8	1.1	43.9	48.3	4.8	53.1	44.8	10.5	55.3	42.2	
Adcirca	9.6	—	9.6	23.6	—	23.6	14.6	—	14.6	8.1	
Other	—	—	—	—	—	—	—	—	—	—	
Total revenues	$354.3	$24.8	$379.1	$411.7	$34.8	$446.5	$412.1	$32.6	$444.7	$386.1	$

(1) Net product sales include both the drug product and the respective inhalation device.
(2) Net product sales include sales of infusion devices including the Remunity Pump.

Category: Earnings

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Dewey Steadman at (202) 919-4097

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Safety and Tolerability of High-dose Inhaled Treprostinil in Pulmonary Hypertension

Kishan S. Parikh, MD[1], **Sudarshan Rajagopal, MD, PhD**[1], **Terry Fortin, MD, MS**[1], **Victor F. Tapson, MD**[2], and **Abby D. Poms, RRT**[1]

[1]Department of Medicine, Duke University Medical Center, Durham, USA

[2]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, USA

Abstract

Pulmonary arterial hypertension (PAH) has emerging therapeutic options including prostacyclin analogs. Inhaled therapy offers advantages compared to alternative routes of administration. We aimed to determine the safety and tolerability of inhaled treprostinil (iTRE) titrated to target maintenance dose higher than the labeled dose for PAH. Our study included 80 consecutive patients (69% female, 70% White) followed at Duke University Medical Center prescribed iTRE at dose > 9 breaths (54 mcg). Etiology of PH was most frequently pulmonary arterial hypertension (PAH) (51%) or secondary to lung disease (35%). Median follow-up was 20.3 months (IQR 14.2–33.2). Most patients (91%) had titrated iTRE dose to 12 breaths (72 mcg) four times daily. Common side effects reported with drug initiation were cough (41%), headache (28%) and throat irritation (8%); the majority of side effects improved at follow-up. Overall, 25% patients discontinued iTRE: 9 transitioned to parenteral therapy, 4 had untolerable side effects, 3 died, and 4 had other reasons. Overall, iTRE taken at a higher dose than approved for use in PAH was safe and well-tolerated in our cohort of PH patients.

Keywords

pulmonary hypertension; treprostinil; prostacyclin analog; inhaled therapy; optimal dose; Tyvaso

Introduction

Pulmonary hypertension (PH) is defined hemodynamically as mean pulmonary arterial pressure greater than 25 mmHg at rest. Whether it occurs as a primary disease of the pulmonary arteries (pulmonary arterial hypertension [PAH], World Health Organization [WHO] Group 1) or secondary to left heart disease, lung disease, chronic thromboembolic disease, or other causes (WHO Groups 2–5, respectively), the diagnosis of PH portends a poor prognosis. The pathogenesis of PAH is directly related to abnormal pulmonary vasculature (i.e., increased vasoconstriction, vascular remodeling, and thrombosis) associated with an imbalance of prostacyclin, endothelin-1, and nitric oxide. (1–3) Current approved therapeutics for PAH target these molecular pathways and fall into one of several

Correspondence to: Kishan S. Parikh, MD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC USA 27710, Phone: 1-919-668-7835, Fax: 1-919-681-9607, Kishan.parikh@dm.duke.edu.

classes: prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators. Occasionally, WHO Groups 2 and 3 patients who have a significant precapillary component of disease are also treated with PAH-specific therapies, although evidence is lacking. (4, 5)

Treprostinil is a tricyclic benzindene prostacyclin analog that is stable at room temperature. (6) As shown in several monotherapy and combination therapy trials, treprostinil in various forms (i.e., parenteral, subcutaneous, and inhaled) improves symptom burden and 6 minute walk distance (6MWD) in PAH patients. (7–16) In particular, compared to parenteral administration, inhaled treprostinil (iTRE) therapy offers the advantage of avoiding long-term invasive access and associated complications, (16, 17) as well as potentially lowering the risk of systemic vasodilation and ventilation-perfusion mismatch in patients with lung disease. (18–20) Inhaled treprostinil was approved for PAH patients with New York Heart Association class III symptoms based on the results of the pivotal Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) trial in 2009, which randomized 235 patients on bosentan or sildenafil to added iTRE (mean dose 50 ± 10 μg) or placebo and showed an increase of 20 meters in 6MWD at 12 weeks in the treatment arm. (13) The currently approved iTRE dosing titration algorithm reaches a maximum of 9 breaths (54 mcg) four times daily.

However, a dose-dependent relationship with duration of pulmonary vascular resistance reduction has been previously shown. (21) Furthermore, iTRE has a half-life of only 44–52 minutes, (22, 23) making optimal dosage with each administration critical. Although doses of up to 12 breaths (72 mcg) four times daily have been reported, the safety and tolerability of > 9 breaths four times daily have not been studied. (7, 8) Of note, iTRE has not been FDA approved for WHO groups II–V. We aimed to characterize safety and tolerability of higher iTRE doses (>9 breaths four times daily and/or greater than 216 mcg/day) from our single tertiary center experience in treating PH patients.

Methods

Study Population

We performed a retrospective cohort study of all WHO Group 1–5 PH patients followed at the Duke University Medical Center PH Clinic prescribed high-dose iTRE (> 9 breaths four times daily) prior to August 2012. The PH clinic standard iTRE dosing protocol is as follows: 3 breaths (18 mcg)/initial session, 6 breaths (36 mcg)/second session, and then titration as tolerated, based on side effects, by 1 breath daily until a maximum dosage of 12 breaths (72 mcg) four times daily is achieved (Figure 1). Of note, iTRE initiation (first and second sessions) was performed in clinic under physician supervision with 4 hours in between the sessions.

Data Sources

Data were collected by chart abstraction from the electronic medical record for three separate time points for each patient: 1) Baseline at 9 breaths four times daily (up to 3 months prior to beginning iTRE); 2) Follow-up 1 (3–6 months post initiation of high-dose

iTRE), and Follow-up 2 (most recent visit prior to August 2012). If a patient stopped high-dose iTRE (either dose reduced or stopped completely) prior to Follow-up 1 or Follow-up 2, data were collected from the most recent visit closest to the high-dose discontinuation. Patient demographics, past medical history, and WHO classification of PH were collected for each patient from the Baseline visit. Start date and initial and subsequent iTRE doses were also obtained for each patient. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Duke University Medical Center.

Endpoints

The primary endpoints for our study were safety and tolerability. Safety parameters consisted of adverse events (AEs), routine clinical laboratory tests (serum creatinine, hematocrit, platelet count), vital signs (pulse, respiratory rate, systolic and diastolic blood pressure, body mass index), and physical examination findings (jugular venous distension, lung sounds, peripheral edema, ascites). Tolerability of high-dose iTRE was assessed by a need for dose reduction, discontinuation, and reasons for discontinuation.

In addition, the following data related to PH severity were captured for all visits: 6MWD, Borg Dyspnea Index, Dyspnea-Fatigue Index, WHO or NYHA functional class, echocardiographic findings, pulmonary function test (PFT) values, amino-terminal pro-B-type natriuretic peptide (NT-proBNP) value, and concomitant PH medications. Statistical analysis of continuous variables was performed with descriptive statistics. Continuous variables were expressed as mean ± standard deviation unless otherwise stated. Student's t-test for paired samples was performed to determine statistical significance of efficacy results. Statistical tests were performed using GraphPad Prism version 5.0a for Mac OS X, GraphPad Softare, La Jolla California USA, www.graphpad.com. Duke University Institutional Review Board determined that the study protocol adheres to ethical principles, and its approval was granted to this study prior to data collection.

Results

A total of 80 patients were included in our study with baseline characteristics described in Table 1. Most patients had PAH (51.9%) or PH secondary to lung disease (31.6%). Dates of iTRE initiation ranged from 12/2005 to 7/2012. Among all patients, the median duration of titration from 9 breaths/dose to 12 breaths/dose was 3 days (25–75% interquartile range [Q1-Q3], 1–3; mean 32.2 days; range 0–685). Median times from start of high-dose iTRE therapy to Follow-up Visits 1 and 2 were 5.2 months (Q1-Q3: 4.0–8.7) and 20.3 months (Q1-Q3: 14.2–33.2), respectively. Finally, of the original cohort, 49 patients had available data for the Follow-up Visit 1 analysis, and 39 patients continued to Follow-up Visit 2.

Adverse Events

Patients at baseline most frequently reported cough (39%) and headache (29%) although both decreased over time. All noted AEs by frequency at Baseline and Follow-up Visits 1 and 2 are listed in Table 2. Additionally, 26 patients (32.5%) had no AE at baseline, and 29 (59.2%) and 25 (64.1%) had no AE at Follow-up Visits 1 and 2, respectively. There were 3 patient deaths attributed to worsening PH or post-operative complications.

Tolerability

Of the total cohort, 78 patients had titrated their dose to 12 breaths (72 mcg) four times daily, while two received 10–11 breaths. During the study period, 15/78 (19.2%) patients decreased the iTRE dose below 12 breaths four times daily due to intolerable medication side effects (Table 3). Of these patients, 5 eventually discontinued iTRE completely (2 secondary to continued medication intolerance at lower dose and 3 required parenteral prostacyclin therapy). Overall, 20/78 (25.6%) patients discontinued iTRE in follow-up: 9 transitioned to parenteral therapy, 4 stopped due to side effects, 3 died, 2 self-discontinued, 1 had worsening PH symptoms on high-dose iTRE (parenteral therapy not appropriate), and 1 had lack of clinical response.

Efficacy Parameters

Routinely used measures including 6-minute walk distance, Borg dyspnea index, and NT-proBNP were tracked over time as biomarkers of PH severity. The average change in 6-minute walk distance was 3.9 meters (95% confidence interval: −13.4, 21.2) from Baseline to Follow-up 1 (n=39; p=0.65), and 31.6 meters (−3.8, 67.0) from the Baseline to Follow-up 2 (n=34; p=0.08). Mean Borg Dyspnea Index changed by −0.2 (−0.7, 0.2) (n=37; p=0.31) and 0.0 (−0.76, 0.76) (n=32; p=1.00) between corresponding visits. Finally, NT-proBNP decreased by 39 ng/L (−312, 234) at Follow-up 1 (n=32, p=0.77) and 630 ng/L (−1456, 197) at Follow-up 2 (n=23, p=0.13).

Discussion

We found that adverse events in PH patients on iTRE at 12 breaths (72 mcg) four times daily were relatively few and this dose was generally well-tolerated. Approximately one-third of our patient population did not experience any untoward effects. Of patients requiring dose reduction, cough and/or headache were responsible in 42% of the cases. Furthermore, among the patients who discontinued iTRE, only 20% cited intolerable side effects. Instead, the most common reason for discontinuation was the need to transition to parenteral therapy for worsening PH.

We found the safety profile of high-dose iTRE to be comparable to prior cited adverse effect/event rates of iTRE therapy. For example, in the TRIUMPH study of 235 patients on iTRE (maximum dose 9 breaths four times daily), cough (54% of patients) and headache (41% of patients) were the most frequent AEs in a 12 week follow-up period. (13) Furthermore, our cohort of patients did not experience previously documented rates of throat irritation (14%) and pharyngolaryngeal pain (11%). Instead, we observed a decrease in throat irritation over time among patients who remained on the drug (7.5% to 2.0% and 0.0% in follow-up visits), and only 2 patients cited throat irritation as a reason for discontinuation. To provide a longer-term profile and outcomes assessment of these patients, the TRIUMPH study open-label extension cohort of 206 patients was followed to 24 months. (7) Mean iTRE doses were 7.8 ± 2.9, 8.9 ± 2.5, 9.4 ± 2.6, and 9.5 ± 2.6 breaths at 6, 12, 18, and 24 months, respectively. Adverse effects (cough and headache) accounted for 6% of events resulting in discontinuation in this longer-term follow-up.

In a sick patient population with significant functional limitations and poor reserve, rapid titration of therapy to optimal dose (one that provides increased efficacy with tolerable side effects) is a critical part of management whenever possible. In prior studies, titration has spanned 18–21 days to achieve a dose of 9 breaths. (8, 13) It is possible that a more aggressive approach when appropriate may be preferred and well-tolerated.

The iTRE delivery system allows for titration of medication beyond the recommended package insert dosing instructions. Thus, PH clinicians can vary dosing for individual patients similar to standard practice with intravenous and subcutaneous prostacyclin therapies. This allows for patient-specific medication titration to maximal clinical benefit while minimizing side effects. Finally, we report a favorable safety and tolerability profile among PH WHO group 3 patients in our study for whom there are currently no approved therapies, and iTRE may provide benefit in this patient population.

Limitations

This study was limited by the retrospective study design and only included patients thought to be good candidates for higher dose iTRE. Because this was an observational study in clinical practice it also suffers from follow-up loss. The iTRE dosing changes were made according to a standardized protocol that resulted in most patients achieving target dose in a few days. In this analysis we did not assess the association of high-dose iTRE with the adjustment of other medications such as diuretics. There were insufficient follow-up data to analyze efficacy endpoints.

Conclusions

In conclusion, iTRE appears to be safe and generally well-tolerated at doses > 9 breaths four times daily among PH patients in our single center experience. These results warrant further investigation into the efficacy of high-dose iTRE in PH.

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Figure 1.
High-dose inhaled treprostinil titration protocol.

Table 1

Baseline Characteristics of Study Population (*n*=80). Continuous variables are expressed as mean±standard deviation.

Patient Characteristic	
Mean age (years)	63.1
Female (%)	55 (68.8)
White (%)	55 (68.8)
Body Mass Index (kilogram/meter^2) Comorbid conditions	30±7.0
• Left heart disease	17 (21.3)
• Diabetes mellitus	18 (22.5)
• Hypertension	36 (45.0)
• Depression	4 (5.0)
• Obesity	25 (31.3)
• Obstructive sleep apnea	20 (25.0)
• Renal disease	11 (13.8)
• Interstitial lung disease/ pulmonary fibrosis	20 (25.0)
• Obstructive lung disease	23 (28.8)
• Sarcoidosis	2 (2.5)
• Venous thromboembolic disease	11 (13.8)
• Non-skin cancer	9 (11.3)
PH World Health Organization Classification	
• Group 1	41 (51.9)
◦ Idiopathic	16 (40.0)
◦ Familial	1 (2.5)
◦ Drug/toxin-induced	2 (5.0)
◦ Connective tissue disease	15 (37.5)
◦ Human Immunodeficiency Virus	2 (5.0)
◦ Portopulmonary hypertension	1 (2.5)
◦ Congenital heart disease	3 (7.5)
• Group 2	3 (3.8)
• Group 3	25 (31.6)
◦ Obstructive disease	13 (52.0)
◦ Interstitial lung disease/fibrosis	6 (24.0)
◦ Mixed pattern	6 (24.0)
• Group 4	9 (11.4)
• Group 5	1 (1.3)
Concomitant pulmonary hypertension medications	
• Endothelin receptor antagonist	46 (57.5)
• Phosphodiesterase-5 inhibitor	53 (66.3)
• Oxygen (continuous)	46 (57.5)
Biomarkers	
World Health Organization Functional Class III/IV	62 (77.5)

Patient Characteristic	
Bo Borg Dyspnea Index Score core	3.6±2.2
Mean 6-minute walk distance (meters)	302±135
NT-proBNP (ng/L) (reference range < 125)	1923±3086

Table 2

Adverse Events at Baseline (9 breaths/dose) and Follow-up Visits.

Adverse effect	Baseline (%) (*n*=80)	Follow-up 1 (%) (*n*=49)	Follow-up 2 (%) (*n*=39)
Cough	31 (38.8)	10 (20.4)	7 (17.9)
Headache	23 (28.8)	7 (14.3)	5 (12.8)
Other	16 (20.0)	4 (8.2)	5 (12.8)
Flushing	13 (16.3)	2 (4.1)	3 (7.7)
Nausea/vomiting	6 (7.5)	0 (0.0)	2 (5.1)
Throat irritation	6 (7.5)	1 (2.0)	0 (0.0)
Diarrhea	5 (6.3)	3 (6.1)	3 (7.7)
Lightheadedness	4 (5.0)	3 (6.1)	0 (0.0)
Syncope	1 (1.3)	0 (0.0)	0 (0.0)
Hypotension	1 (1.3)	0 (0.0)	1 (2.6)

Table 3

Reasons for dose reduction in high-dose iTRE cohort (15/80 patients).

Adverse Effect	Number of Occurrences
Headache	6
Cough	4
Throat irritation	2
Jaw pain	2
Diarrhea	2
Tremulousness	2

EXHIBIT 35

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PULMONARY HYPERTENSION

Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease

Mariana Faria-Urbina[1,2] · Rudolf K. F. Oliveira[1,2,3] · Manyoo Agarwal[4] · Aaron B. Waxman[1,2,5]

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Abstract

Purpose Pulmonary hypertension (PH) in the setting of parenchymal lung disease adversely affects quality of life and survival. However, PH-specific drugs may result in ventilation/perfusion imbalance and currently, there are no approved PH treatments for this patient population. In the present retrospective study, data from 22 patients with PH associated with lung disease treated with inhaled treprostinil (iTre) and followed up clinically for at least 3 months are presented.

Methods PH was defined by resting right heart catheterization as a mean pulmonary artery pressure (mPAP) ≥ 35 mmHg, or mPAP ≥ 25 mmHg associated with pulmonary vascular resistance ≥ 4 Woods Units. Follow-up evaluation was performed at the discretion of the attending physician.

Results From baseline to follow-up, we observed significant improvement in functional class ($n = 22$, functional class III-IV 82 vs. 59%, $p = 0.041$) and 6-min walk distance ($n = 11$, 243 ± 106 vs. 308 ± 109; $p = 0.022$), without a deleterious effect on resting peripheral oxygen saturation ($n = 22$, 92 ± 6 vs. 94 ± 4; $p = 0.014$). Most of the patients (86%, $n = 19/22$) were using long-term nasal supplemental oxygen at baseline. During follow-up, only one patient had increased supplemental oxygen requirement. The most common adverse events were cough, headache, and diarrhea. No severe adverse event was reported.

Conclusions The results suggest that iTre is safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling in terms of functional class, gas exchange, and exercise capacity. Additionally, iTre was well tolerated. The potential role of PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies.

Keywords Pulmonary hypertension · Lung disease · Treprostinil · Exercise capacity

Mariana Faria-Urbina, Rudolf K. F. Oliveira contributed equally to the study.

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✉ Aaron B. Waxman
abwaxman@bwh.harvard.edu

1 Pulmonary and Critical Care Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

2 Center for Pulmonary Heart Disease, Heart & Vascular Center, Brigham and Women's Hospital, Boston, MA, USA

3 Division of Respiratory Diseases, Department of Medicine, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

4 Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

5 Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, PBB Clinics-3, Boston, MA 02115, USA

Introduction

Pulmonary hypertension (PH) in the setting of parenchymal lung disease, termed as World Health Organization (WHO) Group 3 PH, is frequently encountered and adversely affects patients' quality of life and survival [1–3]. Among Group 3 PH, the most common etiologies are chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and combined pulmonary fibrosis and emphysema (CPFE) [4].

It has been shown that pulmonary vascular remodeling is a major contributor to Group 3 PH [5], being mainly characterized by changes in the media, as opposed to Group 1 PH where intima and media remodeling predominate [6]. However, animal models of hypoxia-induced PH have shown heterogeneity of findings in intimal thickness with increasingly elevated mean pulmonary arterial pressure (mPAP) levels [7]. Additionally, in COPD with severe PH, medial and intimal fibrosis and even plexiform lesions have been described, findings similar to Group I PH [8].

Despite the poor survival, compromised functional capacity, and reduced quality of life in Group 3 PH, there are no approved PH treatments for this patient population [1]. This is mainly because in patients with parenchymal lung disease, PH-specific drugs may result in ventilation/perfusion (V/Q) imbalance, particularly in the setting of significant oxygen deficit [9]. However, previous studies have shown improvement in hemodynamics without deleterious effect on gas exchange in patients with Group 3 PH treated with endothelin receptor antagonists and phosphodiesterase-5 inhibitors [10, 11]. Conversely, previous clinical trials with ambrisentan [12] in idiopathic pulmonary fibrosis (IPF) and riociguat (NCT02138825) were terminated due to worse outcome when compared to placebo in Group 3 PH.

Among the available PH-specific drugs, prostacyclin is known to lower mPAP, increase cardiac output, and reduce pulmonary vascular remodeling through its effect on vascular smooth muscle proliferation [13]. Additionally, prostacyclin has demonstrated antiapoptotic properties in the pulmonary vasculature after chronic cigarette smoke exposure [14], and in an animal model of bleomycin-induced pulmonary fibrosis, prostacyclin prevented fibroblast proliferation and showed a protective effect against deterioration of lung function [15]. Furthermore, previous reports have suggested that Iloprost, a prostacyclin analogue, may represent a safe option in Group 3 PH as it is delivered directly to well-ventilated lung units, reducing undesirable alterations in perfusion and subsequently preserving V/Q matching [16].

Treprostinil, a chemically stable tricyclic analogue of prostacyclin, is approved for the treatment of Group 1 PH via subcutaneous, intravenous, inhaled (as treprostinil sodium), or oral (as treprostinil diolamine) routes of administration [1]. It provides sustained pulmonary vasodilation thanks to its longer plasma half-life [17] and specific tissue-binding characteristics [18]. In the present study, we present our experience with the use of inhaled treprostinil (iTre) in 22 WHO Group 3 PH patients who were followed up clinically for at least 3 months after initiation of therapy. We hypothesize that iTre vasodilates well-ventilated lung areas, preserving V/Q matching when administered in PH associated with lung disease.

Methods

Design and study population

In this single-center retrospective observational study, data from 72 patients evaluated at the Pulmonary Vascular Disease (PVD) Clinic at the Brigham and Women's Hospital (Boston, MA, USA) and treated with iTre from December 2009 to November 2016 were reviewed to identify patients with lung disease, based on pulmonary function test (PFT) and high-resolution computed tomography (HRCT) scans of the lungs, and PH with evidence of pulmonary vascular remodeling as defined below. This retrospective analysis was approved by the Partners Human Research Committee.

Lung disease was defined by as follows: (1) COPD: post-bronchodilator FEV1/FVC < 0.7 [19] and/or evidence of emphysema on HRCT; (2) ILD: presence of fibrosis, defined as reticular septal thickening associated with architectural distortion with traction bronchiectasis, or honeycombing on HRCT [20, 21]; (3) CPFE: presence of emphysema and diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT [22].

PH was defined by resting right heart catheterization (RHC) as a mPAP ≥ 35 mmHg (severe PH) [23] or a mPAP ≥ 25 mmHg associated with pulmonary vascular resistance (PVR) ≥ 4 Woods Units (WU). No patients with isolated postcapillary PH (i.e., high PAWP and normal PVR) were included in the study.

Exclusion criteria included the following: identification of another known cause of PH (such as chronic thromboembolic disease); follow-up < 3 months; treatment with another PH-specific drug added in a period < 3 months from iTre initiation; lung transplantation during follow-up (< 3 months); recent hospitalization due to unstable lung disease (≤ 1 month), extemporaneous RHC, and/or inability to review baseline PFT or RHC data.

Treatment regimen and follow-up

All patients consented to receive treatment based on medical judgment [23] after being informed of the potential risks and benefits of iTre. Patients received iTre at three breaths (18 μg) four times daily (72 μg/day). iTre doses were increased as tolerated by three additional breaths (18 μg) per dosing session every 3–7 days to achieve a dose of at least 9–12 breaths or more (≥ 54 μg) four times daily (≥ 216 μg/day) unless limited by side effects. If patients had dose-limiting side effects, then either a slower dose titration or a lower goal dose was prescribed. All patients were on optimized therapies for the treatment of baseline lung disease prior to consideration for iTre treatment, were followed for at least 3 months, and were compliant with the medication. Therapies related to the underlying lung disease were continued throughout the observation period.

Follow-up was performed at the discretion of the attending physician, using WHO functional class (WHO-FC), pulse oxygen saturation (SpO_2), and supplementary oxygen requirement, in addition to at least one of the following tests: resting echocardiography, 6-min walking test (6MWT), and/or 3-min step test with a portable metabolic cart (Shape Medical Systems, Inc., St. Paul, MN, USA), and/or resting RHC. Functional class was systematically estimated by the

treating physician at each visit. Adverse events and discontinuation of iTre were also assessed.

Statistical analysis

Data are presented as mean ± standard deviation or as absolute numbers, unless otherwise stated. The distribution of continuous variables was evaluated using Shapiro–Wilk test. Comparisons between parameters obtained at baseline and during follow-up were performed using paired *t* test or Wilcoxon signed-rank test, as appropriate. $p < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS software, version 19 (IBM Company, Armonk, NY, USA).

Results

Baseline characteristics

Out of 72 patients receiving iTre, 67 had PH with evidence of pulmonary vascular remodeling (per the criteria described above), of which 61 had lung disease. Thirty-nine patients were excluded due to recent hospitalization due to unstable lung disease ($n = 8$), lung transplantation during follow-up ($n = 1$), PH related to chronic thromboembolic pulmonary disease ($n = 1$), initiation of other PH-specific drug in a period < 3 months from iTre initiation ($n = 17$), extemporaneous and/or unretrievable RHC ($n = 7$), and missing clinical/functional data at baseline ($n = 5$). Therefore, the study population was constituted by 22 Group 3 PH patients (Fig. 1).

The mean age was 66 ± 10 years (14 males and 8 females). Eight patients (36%) had COPD, nine (41%) had ILD, and five (23%) were classified as having CPFE. Of the nine ILD patients, two had associated connective tissue disease. Nineteen patients (86%) were using long-term nasal supplemental oxygen therapy at baseline. Eighteen patients (82%) were in WHO-FC III-IV. The mPAP, pulmonary arterial wedge pressure (PAWP), and PVR for the entire population were 44 ± 10 mmHg, 10 ± 4 mmHg, and 8.1 ± 3.6 WU, respectively. Sixteen (73%) of the subjects had severe PH (mPAP ≥ 35 mmHg). Twenty-two (100%) patients had PVR > 4 WU. Three patients had PAWP > 15 mmHg (16–18 mmHg), but they additionally had PVR > 4 WU and therefore, were considered to have PVD as the predominant physiopathologic mechanism for PH. At baseline, the mean 6MWT distance was 242 ± 99 m. Ventilatory efficiency was evaluated by the step test with a portable metabolic cart, showing a baseline VE/VCO_2 *slope* of 46.6 ± 20.1. The baseline characteristics of the 22 patients of the study are summarized in Table 1.

Follow-up assessment

Follow-up information is presented in Fig. 1 and Table 2. The mean final dose of iTre for the entire study cohort was 274 ± 103 µg/day and 82% of the patients ($n = 18/22$) achieved a target dose > 216 µg/day. None of the patients were undergoing pulmonary rehabilitation during the assessment period.

There was significant improvement in WHO-FC (Fig. 2) and no deleterious effect on SpO_2 (Table 2). Only one patient had increased supplemental oxygen requirement after iTre was started. No significant differences were observed in PFT and resting echocardiography after treatment with iTre. Eleven patients with follow-up 6MWT showed significant improvement in the distance walked (Table 2), regardless of iTre being added as the first or second PH-specific drug (Fig. 3). There were no significant changes among the 13

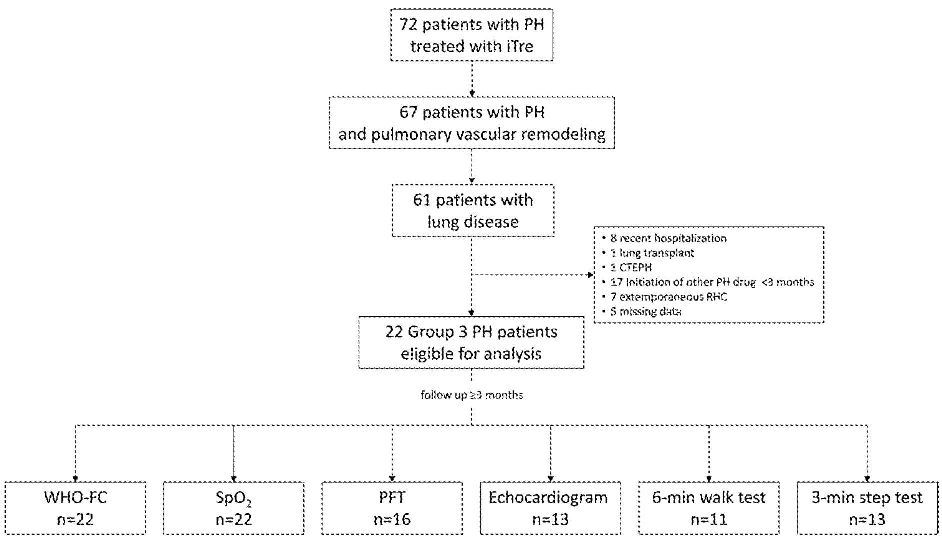

Fig. 1 Study flow diagram. *iTre* inhaled treprostinil sodium, *PH* pulmonary hypertension (mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg and PVR ≥ 3 Woods Units on resting RHC), *CTEPH* chronic thromboembolic pulmonary hypertension, *RHC* right heart catheterization, *WHO-FC* World Health Organization functional class, SpO_2 pulse oxygen saturation, *PFT* pulmonary function test, *RHC* right heart catheterization

Table 1 Baseline characteristics of group 3 pulmonary hypertension patients treated with inhaled treprostinil ($n = 22$)

Variable	Value
Age, years	66 ± 10
Male/female (*n*)	14/8
Body mass index	26.7 ± 4.2
WHO functional class I/II/III/IV (*n*)	0/4/15/3
SpO_2 at rest (%)	92 ± 6
Lung disease n (%)	
Chronic obstructive pulmonary disease	8 (36)
Interstitial lung disease	9 (41)
Combined pulmonary fibrosis and emphysema	5 (23)
Pulmonary function test*	
FEV_1 (L)	1.7 ± 0.8
FEV_1 (% predicted)	61 ± 29
FVC (L)	2.4 ± 1.0
FVC (% predicted)	64 ± 28
FEV1/FVC	72 ± 13
FEV1/FVC (% predicted)	93 ± 17
TLC (L)	5.1 ± 0.8
TLC (% predicted)	71 ± 18
D_LCO (%)	32 ± 6
Echocardiography	
LA AP diameter (mm)	35 ± 7
LVEF (%)	60 ± 6
TRV (m/s)	3.7 ± 0.5
Estimated sPAP (mmHg)	60 ± 16
Right heart catheterization	
RAP (mmHg)	9 ± 6
mPAP (mmHg)	44 ± 10
PAWP (mmHg)	10 ± 4
TPG (mmHg)	33 ± 10
CO (L/min)	4.7 ± 1.3
CI ($L/min/m^2$)	2.5 ± 0.6
PVR (WU)	7.8 ± 3.4
6-min walk test†	
Distance (m)	242 ± 99
Final dyspnea Borg score	6 ± 2
Final SpO_2 (%)	83 ± 8
3-min step test with metabolic cart‡	
VE/VCO_2 slope	46.6 ± 20.1
Δ $P_{ET}CO_2$ (mmHg)	−0.7 ± 2.6
Final SpO_2 (%)	80 ± 8

Data are presented as *n*, *n* (%) or mean ± SD.

WHO World Health Organization, *SpO_2* arterial oxygen saturation measured by pulse oximetry, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *TLC* total lung capacity, *D_LCO* diffusing capacity of the lung for carbon monoxide, *LAAP* left atrial antero-posterior, *LVEF* left ventricular ejection fraction, *TRV* tricuspid regurgitant jet velocity, *sPAP* systolic pulmonary arterial pressure, *RAP* right atrial pressure, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *TPG* transpulmonary gradient, *CO* cardiac output, *CI* cardiac index, *PVR* pulmonary vascular resistance, *WU* Wood units *VE* minute ventilation, *VCO_2* carbon dioxide production, Δ change in, *$P_{ET}CO_2$* end-tidal carbon dioxide tension

*$n = 10$ for TLC and D_LCO

†$n = 17$

‡$n = 15$

patients reevaluated with step test and a portable metabolic cart (Table 2).

Specifically, out of 22 patients included in our study, 21 improved (or maintained) functional class from baseline to follow-up, after treatment with iTre. Of these 21 patients: 19 improved SpO_2; 10 had follow-up with 6MWT—all of them showing improvement in the distance walked; 12 had follow-up with 3-min step test with metabolic data—6 of them reporting better VE/VCO_2 *slope*. Regarding echocardiographic parameters: 7 out of 11, showed improvement in sPAP.

Three patients with severe PH had follow-up RHC that demonstrated significant improvement in systolic PAP (baseline: 82 ± 13 mmHg; follow-up 57 ± 19 mmHg; $p = 0.042$), a trend toward decreased mPAP (baseline: 51 ± 9 mmHg; follow-up 36 ± 13 mmHg; $p = 0.14$) and a trend toward decreased PVR (baseline: 10.3 ± 4.4 WU; follow-up: 4.0 ± 2.2 WU $p = 0.160$). Individual RHC data are presented in the online supplementary material.

Adverse events were reported in ten patients, including cough ($n = 3$), headache ($n = 2$), diarrhea ($n = 2$), cyanosis ($n = 1$), dyspnea ($n = 1$), and pruritus ($n = 1$). None of the patients reported adverse events severe enough to cause cessation of the treatment.

Discussion

In this retrospective study of patients with Group 3 PH treated with iTre at a specialized PVD center, therapy with iTre significantly improved WHO-FC and 6MWT distance, with no significant changes in resting SpO_2 and supplemental oxygen therapy requirement during follow-up. iTre was well tolerated, with cough being the most commonly reported adverse event. Taken together, the current findings suggest that iTre might be a therapeutic option in patients with Group 3 PH, since iTre may improve perfusion to areas where the ventilation is preserved, improving therefore V/Q matching.

The presence of PH in patients with lung disease has been shown to be correlated with poor prognosis [4, 24, 25]. In this context, the potential benefit of PH-specific drugs in subjects with lung disease has been assessed in several studies, with conflicting results. One critical question is whether PH-specific drugs may worsen hypoxia in patients with Group 3 PH.

Deleterious effect of inhaled nitric oxide (NO) on gas exchange has been reported in patients with lung disease

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Table 2 Changes in clinical indices from baseline to follow-up after treatment with inhaled treprostinil

	N	Baseline	Follow-up	*p* value
Clinical assessment	22			
WHO functional class I/II/III/IV (n)		0/4/15/3	2/7/12/1	0.041
SpO_2 at rest (%)		92 ± 6	94 ± 4	0.014
Pulmonary function test	16			
FEV_1 (% predicted)		65 ± 27	60 ± 25	0.23
FVC (% predicted)		67 ± 26	59 ± 22	0.12
FEV_1/FVC (% predicted)		96 ± 15	96 ± 18	0.99
Echocardiography	13			
TRV (m/s)		3.7 ± 0.5	3.6 ± 0.5	0.66
Estimated sPAP (mmHg)		62 ± 18	60 ± 22	0.68
6-min walk test	11			
Distance (m)		243 ± 106	308 ± 109	0.022
Final dyspnea Borg score		6 ± 2	4 ± 2	0.15
Final SpO_2 (%)		82 ± 8	76 ± 9	0.12
3-min step test with metabolic cart	13			
VE/VCO_2 slope		45.9 ± 19.7	47.8 ± 20.1	0.55
Δ $P_{ET}CO_2$ (mmHg)		0.0 ± 1.9	-0.9 ± 2.6	0.081
Final SpO_2 (%)		81 ± 8	80 ± 7	0.76

Data are presented as *n* or mean ± SD

WHO World Health Organization, *SpO_2* arterial oxygen saturation measured by pulse oximetry, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *TRV* tricuspid regurgitant jet velocity, *sPAP* systolic pulmonary arterial pressure, *VE* minute ventilation, *VCO_2* carbon dioxide production, Δ change in, *$P_{ET}CO_2$* end-tidal carbon dioxide tension

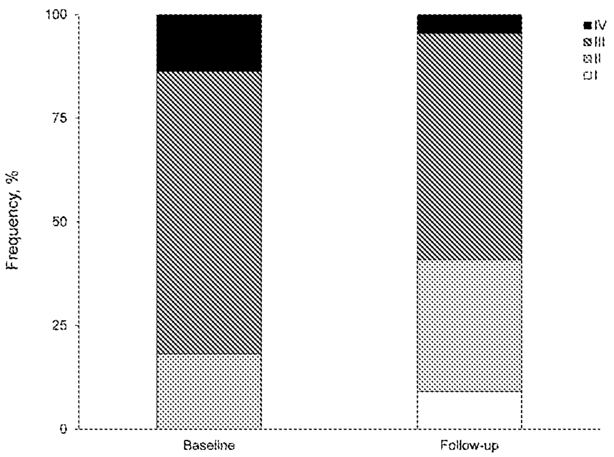

Fig. 2 New York Heart Association functional class changes from baseline to follow-up after treatment with inhaled treprostinil. At baseline, 0, 18, 68, and 14% had functional class I, II, III, and IV, respectively. During follow-up, 9, 32, 55, and 4% had functional class I, II, III, and IV, respectively

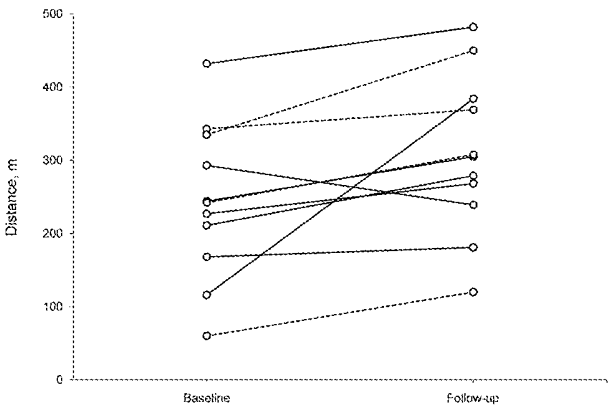

Fig. 3 6-min walk distance changes from baseline to follow-up after treatment with inhaled treprostinil (*n* = 11). Bold lines indicate patients treated with treprostinil monotherapy (*n* = 7). Dotted lines indicate patients treated with dual therapy (treprostinil plus sildenafil or tadalafil, *n* = 4)

and hypoxemia [9]. The results suggest that NO led to dilation of vessels in poorly ventilated lung areas causing reversion of hypoxic vasoconstriction, interfering therefore in the physiologic mechanism by which V/Q matching is achieved in these subjects [9]. Previous studies have reported a negative impact of PH-specific drugs in gas exchange [26, 27] and a clinical trial of ambrisentan in IPF was terminated due to increased risk of disease progression and respiratory hospitalization. However, it is important to mention that only 10% of patients enrolled in this trial had PH [12]. A trial of riociguat in idiopathic interstitial pneumonias was also terminated due to increased risk of death and other serious adverse events as compared to placebo. (NCT02138825). However, others have found

only mild worsening of arterial oxygen tension [28] or even the absence of deleterious effect in gas exchange [10, 11, 16, 29]. In our study, most of the patients (86%) were using supplementary oxygen at baseline, but only one subject experienced increased oxygen requirement after iTre. Additionally, we observed no significant change in resting SpO_2 at follow-up. These findings suggest that iTre might be well tolerated in Group 3 PH.

We also observed significant improvement in WHO-FC and 6MWD. Similar findings have been described previously in a population of ILD patients treated with epoprostenol or bosentan [30]. Additionally, Madden et al. reported the beneficial effect on 6MWD in 7 patients with parenchymal lung disease and PH after treatment with sildenafil [31]. In accordance with our findings, previous reports using parenteral treprostinil in ILD with PH have shown improvement in 6MWT distance and pulmonary hemodynamics without negative impact on systemic oxygen saturation [32]. Additionally, a long-term study in 27 COPD patients with PH treated with different PH-specific drugs supported our observations of significant improvement in functional class and 6MWD [33]. However, in contrast with our results, other reports have described no significant changes in 6MWT distance in lung disease patients after PH-specific treatment [10, 11].

We did not find significant changes in ventilatory efficiency (as measured by VE/VCO_2 *slope*) in a subgroup of 13 patients evaluated with a step test and a portable metabolic cart (a submaximum exercise test). This observation might be reflective of the severity of the lung disease of the studied sample. However, a previous study with inhaled iloprost in COPD and PH described significant improvement in VE/VCO_2 and narrowing of alveolar to arterial oxygen gradient (16), suggesting a better V/Q matching after iloprost inhalation. Therefore, more studies evaluating the effect of inhaled prostacyclin in different populations and in different intensities of exercise (submaximum vs. maximum) are needed to confirm our findings and those of others.

Three patients in our study had follow-up RHC. We observed significant improvement in systolic PAP, a trend toward decreased mPAP and a trend toward decrease in PVR. Previous studies have described significant improvement in hemodynamics when PH-specific drugs were used in Group 3 PH [10, 11, 28]. Others, however, have reported no hemodynamic improvement in severe ILD with PH treated with bosentan [34] and similar negative findings were reported in severe COPD [27].

iTre has been described to have a slow but sustained pulmonary vasodilatory effect, likely secondary to deposit of the drug in the lung after inhalation, followed by subsequent slow release to the pulmonary vascular smooth muscle cells [35]. Therefore, this pharmacodynamic characteristic of iTre might be correlated with our observations. Nevertheless, more studies are needed to evaluate the use of iTre in patients with mild/moderate lung disease and hemodynamically proven severe PH and/or PH with elevated PVR and thus, predominant pulmonary vascular remodeling.

Limitations

This study is limited by its retrospective, single-center, observational, uncontrolled design. Results should be interpreted carefully in view of the small sample size and the heterogeneity of the population (COPD, ILD, and CPFE). However, a subanalysis of each subgroup (Tables S2–S4) demonstrated that the tendency for improved functional class and 6-min walk distance, without significant deleterious effect on SpO_2 that was observed in the entire study population was maintained when analyzing each subcohort. Nonetheless, COPD patients tended to have greater benefit from iTre treatment by the aforementioned parameters. It is possible that our results favoring the potential use of iTRe in Group 3-PH might have been influenced by the presence of pulmonary vascular disease (by study design). However, Group 3 PH with impaired circulatory reserve is of major clinical interest in regard to PH-specific treatment. Additionally, our findings might also be limited by the intrinsic subjective nature of FC assessment, and the lack of a control group. Finally, information about the timing of SpO_2 assessment in relation to the administration of iTre was not available, and therefore, we are not able to comment on the acute effect of iTre on SpO_2.

Conclusion

In this retrospective analysis, we showed that inhaled treprostinil sodium (iTre) was safe in patients with Group 3 PH and evidence of pulmonary vascular remodeling. iTre improved WHO-FC and 6MWT distance, without deleterious effects on resting SpO_2. iTre was well tolerated, with no serious adverse events reported. The potential role of inhaled PH-specific drugs in Group 3 PH should be further assessed in larger prospective studies. Until then, its use in Group 3 PH should be cautiously evaluated in specialized PH Centers, after an individualized assessment and risk–benefit consideration.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval The study protocol was approved by the Partners Human Research Committee (2011P000272).

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EXHIBIT 36

For Immediate Release

United Therapeutics Corporation Announces $1 Billion Accelerated Share Repurchase Program

Repurchase reflects the strength of United Therapeutics' balance sheet and confidence in its near-term prospects

SILVER SPRING, Md. and RESEARCH TRIANGLE PARK, N.C., March 25, 2024: United Therapeutics Corporation (Nasdaq: **UTHR**), a public benefit corporation, today announced that its Board of Directors has authorized the company to purchase up to $1 billion of United Therapeutics' common stock. This program builds on United Therapeutics' planned $400 million paydown of its revolving credit facility in 2024, of which $100 million was paid down during the first quarter of 2024.

To enact the program, United Therapeutics today will enter into an Accelerated Share Repurchase (**ASR**) agreement with Citibank, N.A. (**Citi**) to repurchase $1 billion of the company's common stock.

"We're in a unique position with a solid, growing, and profitable cash-generating business along with the potential to revolutionize the way end-stage organ disease is treated through an unlimited supply of tolerable, transplantable organs," said **Martine Rothblatt, Ph.D.**, Chairperson and Chief Executive Officer of United Therapeutics. "Having learned a great deal through the construction and commissioning of the world's first clinical-scale designated pathogen-free facility to support our xenotransplantation efforts, we are confident in our ability to fund future facilities while balancing prudent capital allocation for all of our stakeholders. The current valuation of United Therapeutics' stock makes repurchases of UTHR shares a solid investment and represents a chance to enhance long-term shareholder value."

Under the terms of the ASR agreement, on March 27, 2024, United Therapeutics will make an aggregate upfront payment of $1 billion to Citi and will receive an initial delivery of shares representing approximately 80% of the total shares that would be repurchased under the ASR agreement measured based on the closing stock price of UTHR's common stock on March 25, 2024. The final number of shares that United Therapeutics will ultimately repurchase pursuant to the ASR agreement will be based on the average of the daily volume-weighted average price per share of United Therapeutics' common stock during the term of the ASR, less a discount and subject to adjustments pursuant to the terms and conditions of the ASR agreement. At final settlement of the ASR agreement, United Therapeutics may be entitled to receive additional shares of United Therapeutics' common stock, or, under certain limited circumstances, be required to make cash payment to Citi or, if United Therapeutics elects, deliver shares to Citi. The final settlement of the ASR is expected to be completed in the second quarter of 2024 with respect to $300 million of the ASR and in the third quarter of 2024 with respect to $700 million of the ASR. As of February 14, 2024, United Therapeutics had approximately 47.1 million shares outstanding.

This press release does not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall it constitute an offer, solicitation, or sale in any jurisdiction in which such offer, solicitation, or sale is unlawful.

United Therapeutics: Enabling Inspiration

At United Therapeutics, our vision and mission are one. We use our enthusiasm, creativity, and persistence to innovate for the unmet medical needs of our patients and to benefit our other stakeholders. We are bold and unconventional. We have fun; we do good. We are the first publicly-traded biotech or pharmaceutical company to take the form of a public benefit corporation (PBC). Our public benefit purpose is to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs.

You can learn more about what it means to be a PBC here: unither.com/pbc.

Forward-Looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, statements related to our confidence in our near-term prospects; the amount of our planned paydown of our revolving credit facility; the growth of our business; our potential to revolutionize the way end-stage organ disease is treated; our ability to fund future facilities; the benefits of the share repurchase to shareholders; our plan to enter into an ASR agreement; the number of shares to be repurchased under the ASR agreement; the timing and manner of the final settlement under the ASR agreement; and our goals of innovating for the unmet medical needs of our patients and to benefit our other stakeholders, furthering our public benefit purpose of developing novel pharmaceutical therapies and technologies that expand the availability of transplantable organs. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of March 25, 2024, and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events, or any other reason.

For Further Information Contact:

Dewey Steadman at (202) 919-4097
https://ir.unither.com/contact-ir/

EXHIBIT 37

VERITEXT
LEGAL SOLUTIONS

Deposition of:

Aaron Waxman , M.D., Ph.D.

January 8, 2022

In the Matter of:

United Therapeutics Corporation vs. Liquidia Technologies (IPR)

Veritext Legal Solutions
800-734-5292 | calendar-dmv@veritext.com |

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

____

LIQUIDIA TECHNOLOGIES, INC.,

Petitioner

vs.

UNITED THERAPEUTICS CORPORATION,

Patent Owner

____

IPR2021-00406

U.S. Patent No. 10,716,793

Remote Videotaped Deposition of

AARON B. WAXMAN, M.D., Ph.D.

January 8, 2022

10:34 a.m.

Reported by: Bonnie L. Russo

Job No. 5008601

Remote Videotaped Deposition of Aaron B. Waxman, M.D., Ph.D. held through:

Veritext Legal Solutions
1250 I Street, N.W.
Washington, D.C.

Pursuant to Notice, when were present on behalf of the respective parties:

APPEARANCES:

On behalf of the Petitioner:

JONATHAN DAVIES, ESQUIRE
COOLEY LLP
1299 Pennsylvania Avenue, N.W.
Suite 700
Washington, D.C. 20004
jdavies@cooley.com
-and-
BRITTANY CAZAKOFF, ESQUIRE
11951 Freedom Drive
1 Freedom Square
Reston Town Center
Reston, Virginia 20190
bcazakoff@cooley.com

On behalf of the Patent Owner:
MANDY KIM, ESQUIRE
McDERMOTT WILL & EMERY
18565 Jamboree Road, Suite 250
Irvine, California 92612
mhkim@mwe.com
-and-
STEPHEN MAEBIUS, ESQUIRE
FOLEY & LARDNER, LLP
321 North Clark Street
Suite 2800
Chicago, Illinois 60654
smaebius@foley.com

Also Present:
Orson Braithwaite, Videographer
Peter Curran, Concierge

I N D E X

EXHIBITS

EXHIBITS (CONTINUED):

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Exhibit 1062	Article entitled "Ultrasonic versus jet nebulization or iloprost in severe pulmonary hypertension"	122
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(Exhibits bound separately.)

P R O E E D I N G S
(10:34 a.m.)
10:34:44
THE VIDEOGRAPHER: Good morning. 10:34:48
We are going on the record at 10:34 10:34:52
a.m. on January 8, 2022. 10:34:55
This is Media Unit 1 of the 10:34:58
remote-recorded deposition of Dr. Aaron Waxman 10:35:01
in the matter of Liquidia Technologies versus 10:35:03
United Therapeutics Corporation filed in the 10:35:07
United States Patent and Trademark Office, 10:35:11
Patent Trial and Appeal Board, Case No. IPR 10:35:16
2021-0046 -- excuse me -00406. 10:35:19
My name is Orson Braithwaite from 10:35:24
the firm Veritext Legal Solutions. I am the 10:35:27
videographer. The court reporter is Bonnie 10:35:29
Russo from the firm Veritext Legal Solutions. 10:35:30
Counsel will now state their 10:35:32
appearances and affiliations for the record. 10:35:34
MR. DAVIES: Jonathan Davies from 10:35:37
Cooley. With me today is my colleague, 10:35:39
Brittany Cazakoff, representing the petitioner, 10:35:44

Liquidia Technologies. 10:35:46

MS. KIM: Mandy Kim with McDermott 10:35:48
Will & Emery on behalf of the patent owner, 10:35:55
United Therapeutics Corporation.

THE VIDEOGRAPHER: Thank you.

Will the court reporter please swear in the witness.

THE COURT REPORTER: Yes. Before I do that I have a quick stipulation to put on the record.

The attorneys participating in this deposition acknowledge that I am not physically present in the deposition room, and that I will be reporting this deposition remotely.

They further acknowledge that, in lieu of an oath administered in person, I will administer the oath remotely.

The parties further agree that if the witness is testifying from a state where I am not a notary, that the witness may be sworn in by an out-of-state notary.

If any party has an objection to

this manner of reporting, please state it now.
(Pause.)
THE COURT REPORTER: Hearing, none we can proceed and I will swear in the witness.

AARON B. WAXMAN, M.D., Ph.D.,
being first duly sworn, to tell the truth, the whole truth, and nothing but the truth, testified as follows:

EXAMINATION BY COUNSEL FOR PETITIONER 10:36:45
BY MR. DAVIES: 10:36:45
Q. Good morning, Dr. Waxman, and thank you for giving us a little bit of your time on a Saturday. 10:36:45 10:36:50 10:36:50
A. Thanks for accommodating me. 10:36:50
Q. Can you state your full name for the record. 10:36:52 10:36:54
A. Aaron B. Waxman. 10:36:55
Q. And can you provide your current address? 10:36:57 10:36:59
A. Home or business? 10:36:59
Q. Home. 10:37:02

to a patient, do you? 11:16:27
A. Not solely, no. 11:16:28
Q. What is the other evidence that you rely on in your clinical practice? 11:16:30 11:16:31
A. Well, that requires not only hemodynamic but also a patient's subjective response to a treatment. 11:16:34 11:16:38 11:16:41
Q. And the patient's subjective response would not include the hemodynamic responses that we have already discussed, correct? 11:16:53 11:16:55 11:16:57 11:16:57
A. I guess it depends on how you define that. 11:17:01 11:17:04
Q. Well, how do you define it, Doctor? 11:17:04
A. Well, I expect there to be a hemodynamic improvement that results in improved blood flow which results in the patient feeling better. 11:17:07 11:17:14 11:17:17 11:17:20
Q. In your experience though it is not always the case that a hemodynamic improvement results in a subjective improvement, correct, in the patient? 11:17:23 11:17:25 11:17:29 11:17:31

A. Not always, no. 11:17:33
Q. And in your clinical practice you would not be able to determine from hemodynamic data alone whether there was a therapeutic benefit to a person suffering from pulmonary hypertension, correct? 11:17:35 11:17:51 11:17:55 11:18:00 11:18:03
A. That I would not agree with. 11:18:04
Q. Okay. Why not? 11:18:06
A. Well, because the disease is quite complicated and it is not just a hemodynamic problem, but the hemodynamics are what define the disease pulmonary hypertension, and if I see a hemodynamic improvement, that likely does result in some improvement. Whether it's a subjective or physiologic improvement, that may be different, but nonetheless, if a patient has hemodynamic improvement, it's likely that their heart function will improve and I would anticipate that their survival will improve. 11:18:07 11:18:13 11:18:15 11:18:15 11:18:25 11:18:25 11:18:28 11:18:29 11:18:32 11:18:35 11:18:38
Q. So let me re-ask the question more specifically. 11:18:41 11:18:44
You are not able to tell based on 11:18:45

hemodynamic data alone whether there would be a subjective improvement in a patient, correct?

MS. KIM: Objection. Asked and answered.

THE WITNESS: Just so I understand the question, are you asking me if a patient has a hemodynamic improvement will they always have a subjective improvement?

BY MR. DAVIES:

Q. That's correct, Doctor.

MS. KIM: Same objection. Asked and answered.

THE WITNESS: I would say the answer is not 100 percent of the time.

BY MR. DAVIES:

Q. So relying on hemodynamic data alone you could not say with certainty that a patient would experience a subjective improvement if they were suffering from pulmonary hypertension, correct?

MS. KIM: Objection. Asked and answered. Mischaracterizes testimony.

THE WITNESS: Not for every patient. 11:19:50
BY MR. DAVIES: 11:19:53
Q. For purposes -- strike that. 11:20:51
So for the definition of therapeutically effective -- strike that. 11:21:16 11:21:20
So the plain and ordinary meaning of therapeutically effective that you applied in your opinions expressed in your two declarations, hemodynamic changes alone could be sufficient to demonstrate therapeutically effectiveness, right? 11:21:22 11:21:29 11:21:30 11:21:32 11:21:37 11:21:44
MS. KIM: Objection. Vague. Mischaracterizes testimony. 11:21:45 11:21:47
THE WITNESS: I think importantly, pulmonary hypertension is a hemodynamic disease and it is defined by hemodynamics, and if you are talking about a drug that is a vasodilator if you don't see a hemodynamic response it would suggest the drug probably doesn't work. Whereas, if you do see a hemodynamic response that would suggest the drug is effective and is worth pursuing. 11:21:49 11:21:51 11:21:57 11:22:00 11:22:04 11:22:07 11:22:10 11:22:13 11:22:17

BY MR. DAVIES: 11:22:20
Q. Does that hemodynamic response that 11:22:20
you just described, Dr. Waxman, does that for 11:22:23
purpose of your analysis of the '793 patent 11:22:26
indicate that the drug is also therapeutically 11:22:30
effective? 11:22:35
A. Yes. 11:22:35
Q. So for purposes of the plain and 11:22:50
ordinary meaning of therapeutically effective 11:22:53
that you applied in your two IPR declarations 11:22:55
you did not need to rely on subjective 11:23:02
improvement data of patients suffering from 11:23:05
pulmonary hypertension, correct? 11:23:09
A. Well, at the time it was not 11:23:10
available from an inhaled standpoint, but it 11:23:15
was from a subcutaneous standpoint. 11:23:19
Q. If you could turn to Page 21 of your 11:23:43
second declaration and let me know when you are 11:24:14
there. 11:24:18
A. I am there. 11:24:20
Q. Okay. And do you see a Footnote 4? 11:24:21
A. Yes. 11:24:27

exercise test with gas exchange so it's an 14:17:20
objective test. 14:17:23
BY MR. DAVIES: 14:17:25
Q. Is there anything else you use to 14:17:26
assess therapeutic effectiveness in the clinic 14:17:27
for PH treatments? 14:17:31
A. I also ask the patient how they are 14:17:33
feeling. 14:17:38
Q. Anything else? 14:17:38
A. Like I said, right heart 14:17:38
catheterization at certain time points. 14:17:43
Q. Anything else? 14:17:46
A. Echocardiography at certain time 14:17:47
points. 14:17:52
Q. Anything else? 14:17:54
A. More and more cardiac MR at certain 14:17:56
time points. 14:18:02
Q. Anything else? 14:18:05
A. I think that is probably everything. 14:18:06
Well, I should add that, 14:18:13
occasionally, we will also check some blood 14:18:15
tests like the NT-proBNP but not routinely. 14:18:18

Q. In the clinic setting you don't rely exclusively on hemodynamic data to assess therapeutic effectiveness, correct? 14:18:24 14:18:31 14:18:35
A. I do not rely exclusively on it, no. 14:18:38
Q. Is it true that you don't rely exclusively on it in the clinical setting because improvements in hemodynamics do not necessarily result in therapeutic effectiveness; is that correct? 14:18:40 14:19:16 14:19:20 14:19:28 14:19:35
MS. KIM: Objection. Mischaracterizes testimony. 14:19:36 14:19:36
THE WITNESS: Yeah, I would say that's not the case. I think that that mischaracterizes what I said earlier. 14:19:37 14:19:39 14:19:41
BY MR. DAVIES: 14:19:43
Q. Okay. How so? 14:19:43
A. Well, we don't do it routinely and visit to visit because it's -- it's an invasive test that is somewhat cumbersome for the patient. It doesn't take very long, and it's a pretty easy test to do, but it means going to the cath lab. 14:19:47 14:19:50 14:19:56 14:19:59 14:20:02 14:20:05

Q. You would agree, though, that in your experience, including with patients taking Tyvaso, that some patients may experience improvements in hemodynamics and not see a corresponding change in other nonhemodynamic measures as you've described that you apply in the clinic, correct? 14:20:08 14:20:10 14:20:13 14:20:17 14:20:23 14:20:26 14:20:29

A. No. 14:20:31

MS. KIM: Objection. Vague. 14:20:31

THE WITNESS: Sorry. No. 14:20:33

MS. KIM: That's okay. 14:20:36

BY MR. DAVIES: 14:20:38

Q. You have patients, Dr. Waxman, on pulmonary hypertension treatments that utilize nebulizers for delivery of the drug, correct? 14:21:27 14:21:37 14:21:40

A. I -- well, yes. 14:21:50

Q. What are the products for treatment of PH that utilize nebulizers for delivery? 14:21:54 14:22:00

A. There are only two that I use and that would include inhaled treprostinil or Tyvaso and epoprostenol which generally we would only use that in the hospital. 14:22:03 14:22:09 14:22:14 14:22:21

EXHIBIT 38

Liquidia

To Whom It May Concern:

Pulmonary hypertension in patients with interstitial lung disease (PH-ILD) remains a progressive and fatal condition that can lead to heart failure and death.

YUTREPIA™ was introduced to the pulmonary hypertension community in 2015 and was the first clinical program to explore the benefits of an inhaled dry powder formulation of treprostinil for pulmonary hypertension patients.

Since that time, TYVASO has become available for the treatment of PH-ILD in nebulized and dry powder formulations. This is a significant step forward for patients suffering from the disease. However, YUTREPIA has some key differences to the profile of TYVASO that may, for at least some patients, lead to improvements in patient outcomes and quality of life.

For instance, YUTREPIA, in part due to its unique PRINT formulation, is the first low-resistance dry powder inhaler, which may be an important attribute for patients with compromised lung function. In addition, YUTREPIA provides patients with a wider and higher range of therapeutic doses, which could allow patients to delay more invasive therapies, such as parenterally administered treprostinil.

Pulmonary hypertension represents a chronic and rare disease. Our patient communities rely on the FDA to approve innovative, safe, and effective treatment to reach those in need. We believe Yutrepia meets these high-quality standards and has the potential to be a critical treatment option for our patients.

Based on these key attributes, we believe Yutrepia offers an important treatment choice for providers and patients and support the recommendation for commercial availability as soon as possible.

Sincerely,

Dr. Hill Dr. Hill (Mar 28, 2024 22:28 EDT)	Dr. Farber Dr. Farber (Mar 28, 2024 11:44 MDT)	JWMcConnell Dr. McConnell (Mar 28, 2024 12:27 EDT)
Nicholas Hill, MD	Harrison Farber, MD	John W. McConnell, MD
Dr. Ravichandran (Mar 28, 2024 16:24 EDT)	Dr. Ricardo Restrepo (Mar 28, 2024 11:21 EDT)	Dr. Jeremy Feldman Dr. Jeremy Feldman (Mar 28, 2024 07:12 PDT)
Ashwin Ravichandran, MD	Ricardo Restrepo-Jaramillo, MD	Jeremy Feldman, MD
Rajan Saggar	Sandeep Sahay	Akram Khan, MBBS Akram Khan, MBBS (Mar 28, 2024 14:07 PDT)
Rajan Saggar, MD	Sandeep Sahay, MD, FCCP	Akram Khan, MD

EXHIBIT 39

EXHIBIT 2

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYVASO safely and effectively. See full prescribing information for TYVASO.

TYVASO (treprostinil) inhalation solution
Initial U.S. Approval: 2002
For Oral Inhalation Only

----------------------------INDICATIONS AND USAGE-------------------------

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance. (1)

----------------------DOSAGE AND ADMINISTRATION---------------------

- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. (2.1)
- Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. (2.1)

---------------------DOSAGE FORMS AND STRENGTHS---------------------

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

-------------------------------CONTRAINDICATIONS--------------------------

None (4)

-----------------------WARNINGS AND PRECAUTIONS---------------------

- Safety and efficacy have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). (5.1)
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. (5.2)
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants. (5.4, 7.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.5, 7.5)
- Hepatic or renal insufficiency may increase exposure and decrease tolerability. (2.2, 2.3, 5.3)

------------------------------ADVERSE REACTIONS----------------------------

Most common adverse reactions (≥ 10%) are cough, headache, nausea dizziness, flushing, throat irritation, pharyngolaryngeal pain and diarrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or via e-mail at drugsafety@unither.com, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

------------------------------DRUG INTERACTIONS----------------------------

- Concomitant diuretics, antihypertensives or other vasodilators may increase the risk of systemic hypotension. (7.1)

-----------------------USE IN SPECIFIC POPULATIONS---------------------

- Pregnancy: Tyvaso should be used only if clearly needed. (8.1)
- Nursing women: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

***Sections or subsections omitted from the full prescribing information are not listed.**

Revised: [July/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

Tyvaso™ (treprostinil) inhalation solution

For Oral Inhalation Only

1 INDICATIONS AND USAGE

Tyvaso is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON-100/7 (an ultrasonic, pulsed-delivery device) and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:

Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:

Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.

The maximum recommended dosage is 9 breaths per treatment session, 4 times daily.

2.2 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Patients with Renal Insufficiency

Plasma clearance of treprostinil may be reduced in patients with renal insufficiency, since treprostinil and its metabolites are excreted mainly through the urinary route. Patients with renal insufficiency may therefore be at increased risk of dose-dependent adverse reactions *[see Warnings and Precautions (5.3), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.4 Administration

Tyvaso must be used only with the Tyvaso Inhalation System. Patients should follow the instructions for use for operation of the Tyvaso Inhalation System and for daily cleaning of the device components after the last treatment session of the day. To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device.

Do not mix Tyvaso with other medications in the Optineb-ir device. Compatibility of Tyvaso with other medications has not been studied.

The Tyvaso Inhalation System should be prepared for use each day according to the instructions for use. One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Avoid skin or eye contact with Tyvaso solution. Do not orally ingest the Tyvaso solution.

3 DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Patients with Pulmonary Disease or Pulmonary Infections

The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

5.2 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso may produce symptomatic hypotension.

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function *[see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]*.

5.4 Risk of Bleeding

Since Tyvaso inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

5.5 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.2)]*.
- Bleeding [*see Warnings and Precautions (5.4)]*.

6.1 Adverse Reactions Identified in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-week placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

Table 1: Adverse Events in ≥ 4% of PAH Patients Receiving Tyvaso and More Frequent* than Placebo

Adverse Event	Treatment n (%)	
	Tyvaso n = 115	**Placebo n = 120**
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

Adverse Events Associated with Route of Administration

Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (Tyvaso); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Tyvaso with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics

7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.5 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.5)]*.

7.6 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity *[see Developmental Toxicity (13.3)]*. Animal reproduction studies are not always predictive of human response; Tyvaso should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Tyvaso did not include patients younger than 18 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Clinical studies of Tyvaso did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Clinical Pharmacology (12.3), Dosage and Administration (2.2) and Warnings and Precautions (5.3)]*.

8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent *[see Clinical Pharmacology (12.3), Dosage and Administration (2.3) and Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

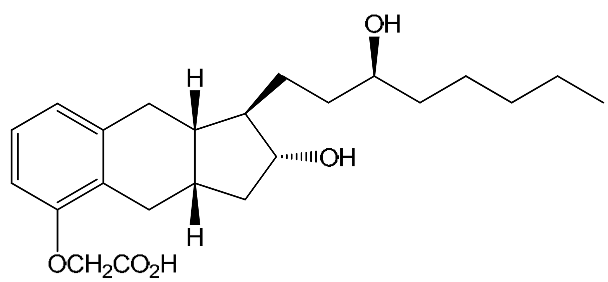
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil intended for administration by oral inhalation using the Optineb-ir device. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules, containing 1.74 mg treprostinil (0.6 mg/mL). Each ampule also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.51 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Pharmacokinetic information for single doses of inhaled treprostinil was obtained in healthy volunteers in three separate studies. Treprostinil systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the doses administered (18 mcg – 90 mcg).

Absorption and Distribution

In a three-period crossover study, the bioavailability of two single doses of Tyvaso (18 mcg and 36 mcg) was compared with that of intravenous treprostinil in 18 healthy volunteers. Mean estimates of the

absolute systemic bioavailability of treprostinil after inhalation were approximately 64% (18 mcg) and 72% (36 mcg).

Treprostinil plasma exposure data were obtained from two studies at the target maintenance dose, 54 mcg. The mean C_{max} at the target dose was 0.91 and 1.32 ng/mL with corresponding mean T_{max} of 0.25 and 0.12 hr, respectively. The mean AUC for the 54 mcg dose was 0.81 and 0.97 hr•ng/mL, respectively.

Following parenteral infusion, the apparent steady state volume of distribution (V_{ss}) of treprostinil is approximately 14 L/70 kg ideal body weight.

In vitro treprostinil is 91% bound to human plasma proteins over the 330-10,000 mcg/L concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

The elimination of treprostinil (following subcutaneous administration of treprostinil) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model.

Special Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Dosage and Administration (2.2), Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Renal Insufficiency

No studies have been performed in patients with renal insufficiency; therefore, since treprostinil and its metabolites are excreted mainly through the urinary route, there is the potential for an increase in both parent drug and its metabolites and an increase in systemic exposure *[see Dosage and Administration (2.3), Warnings and Precautions (5.3) and Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human sc infusion rate (1.25 ng/kg/min) and 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

13.3 Developmental Toxicity

In pregnant rats, continuous sc infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the recommended starting human sc infusion rate and about 16 times the average rate achieved in clinical trials, on a ng/m^2 basis), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous sc infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar vertebra 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human sc infusion rate and 5 times the average rate achieved in clinical trials, on a ng/m^2 basis).

13.4 Inhalational Toxicity

Rats and dogs that received daily administrations of treprostinil by inhalation for 3 months developed respiratory tract lesions (respiratory epithelial degeneration, goblet cell hyperplasia/hypertrophy, epithelial ulceration, squamous epithelial degeneration and necrosis, and lung hemorrhage). Some of the same lesions seen in animals sacrificed at the end of treatment (larynx, lung and nasal cavity lesions in rats, and lesions of the larynx in dogs) were also observed in animals sacrificed after a 4-week recovery period. Rats also developed cardiac changes (degeneration/fibrosis). A no-effect dose level for these effects was not demonstrated in rats (doses as low as 7 µg/kg/day were administered); whereas 107 µg/kg/day was a no-effect dose level in dogs.

14 CLINICAL STUDIES

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group I), nearly all with NYHA Class III symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/familial (56%), secondary to collagen vascular disease (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 (p<0.001). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

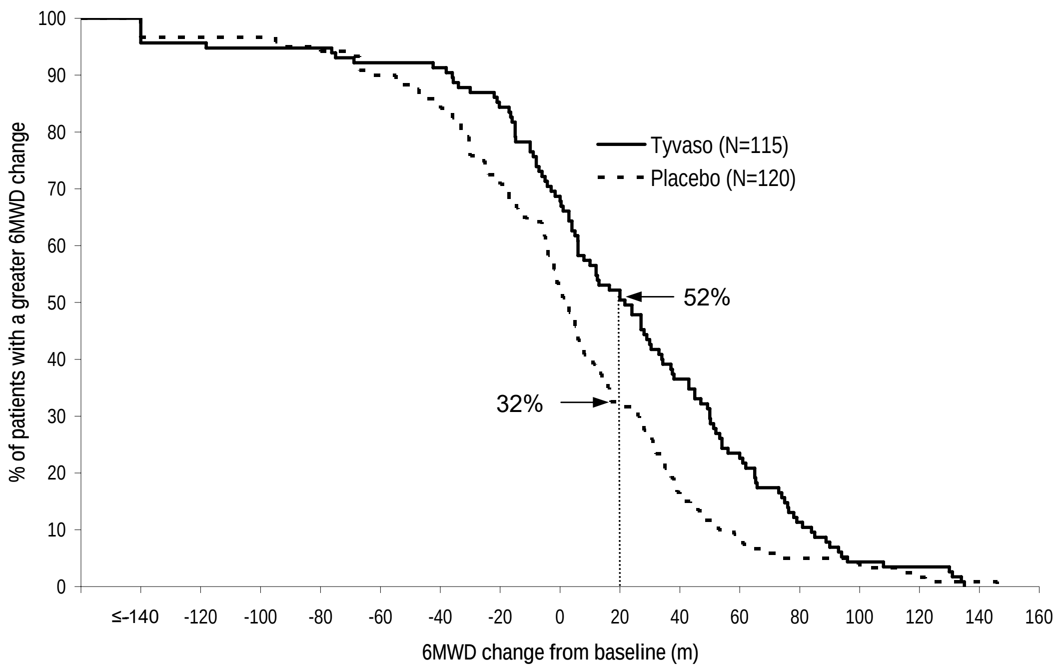


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

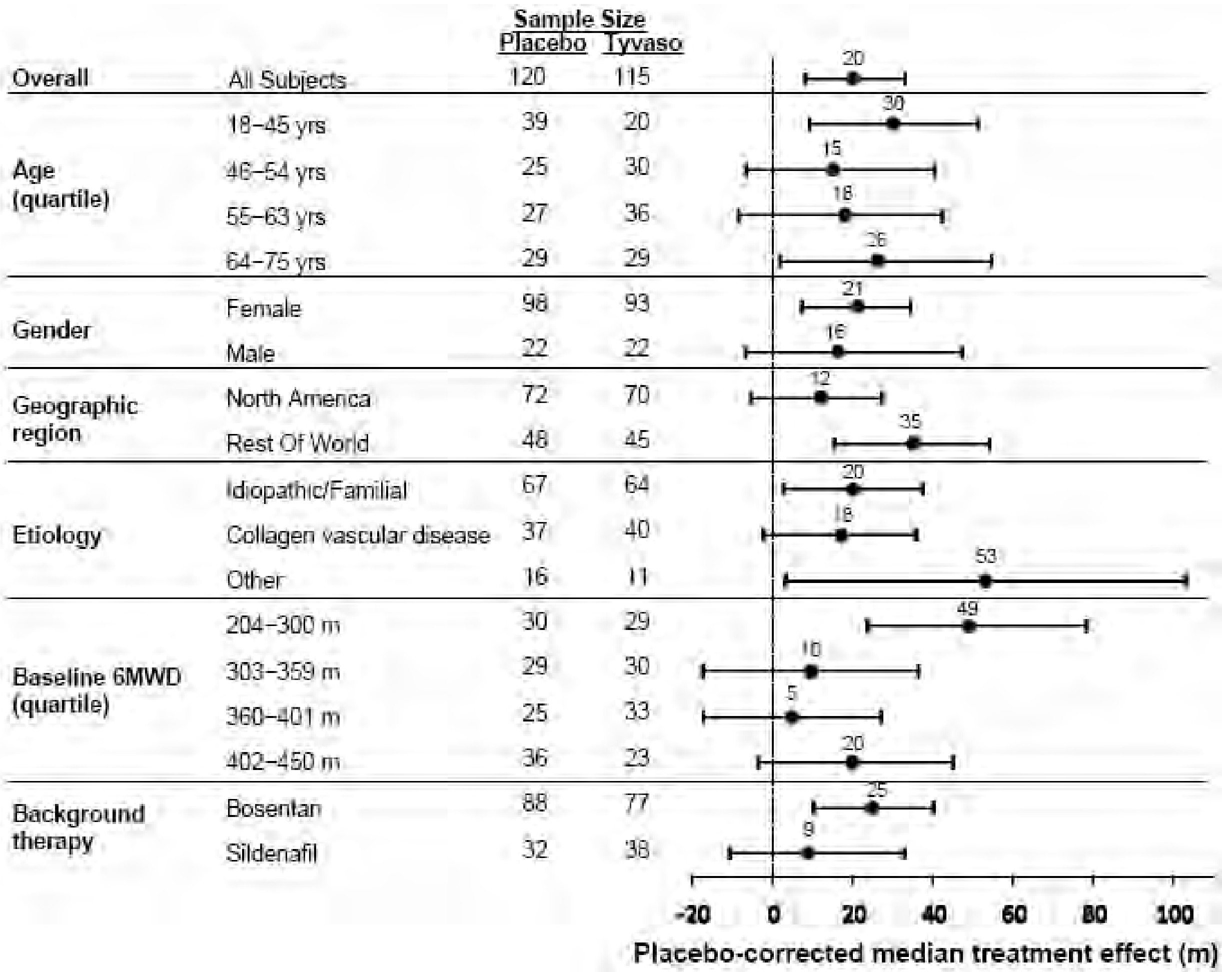


Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

16 HOW SUPPLIED/STORAGE AND HANDLING

Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as four ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL.

Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days. Because Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch.

One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than one day (24 hours). Any remaining solution should be discarded at the end of the day.

Tyvaso Inhalation System Starter Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-01)

Tyvaso Inhalation System Refill Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and accessories. (NDC 66302-206-02)

2.9 mL LDPE ampule containing 1.74 mg treprostinil (0.6 mg per mL), carton containing 1 foil pouch with 4 ampules. (NDC 66302-206-03)

17 PATIENT COUNSELING INFORMATION

Patients should be properly trained in the administration process for Tyvaso, including dosing, Optineb-ir device set up, operation, cleaning, and maintenance, according to the instructions for use *[see Dosage and Administration (2.1)]*.

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device *[see Dosage and Administration (2.4)]*.

In the event that a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible *[see Dosage and Administration (2.1)]*.

Patients should avoid skin or eye contact with Tyvaso. If Tyvaso comes in contact with the skin or eyes, instruct patients to rinse immediately with water *[see Dosage and Administration (2.4)]*.

US Patent No. 5,153,222
US Patent No. 6,765,117
US Patent No. 6,521,212
US Patent No. 6,756,033

United Therapeutics Corp.
Research Triangle Park, NC 27709

Tyvaso manufactured by:

Catalent Pharma Solutions
Woodstock, IL 60098

For United Therapeutics Corp.
Research Triangle Park, NC 27709

July 2009

PATIENT PACKAGE INSERT

Tyvaso (Tī-vāsō)

(treprostinil)

Inhalation Solution

Read this Patient Package Insert before you start taking Tyvaso and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is Tyvaso?

Tyvaso is a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Tyvaso can improve the ability to do exercise in people who also take bosentan (an endothelin receptor antagonist (ERA)) or sildenafil (a phosphodiesterase-5 (PDE-5) inhibitor). Your ability to do exercise decreases 4 hours after taking Tyvaso.

It is not known if Tyvaso is safe or effective in people under 18 years of age.

What should I tell my healthcare provider before taking Tyvaso?

Before taking Tyvaso, tell your healthcare provider about all of your medical conditions, including if you:

- have lung disease, such as asthma or chronic obstructive pulmonary disease (COPD)
- have a lung infection
- have liver problems or kidney problems
- have low blood pressure
- are pregnant or plan to become pregnant. It is not known if Tyvaso will harm your unborn baby. Women who can become pregnant should use effective birth control while taking Tyvaso.
- are breast-feeding or plan to breast-feed. It is not known if Tyvaso passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Tyvaso.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tyvaso and other medicines may affect each other.

Especially tell your healthcare provider if you take any of these medicines:

- medicines that decrease blood clotting
- water pills (diuretics)
- medicines used to treat high blood pressure or heart disease
- gemfibrozil (Lopid) (for high cholesterol)
- rifampin (Rimactane, Rifadin, Rifamate, Rifater) (for infection)

Know the medicines you take. Keep a list of them and show it to your healthcare provider and specialty pharmacist when you get a new medicine.

How should I take Tyvaso?

- Take Tyvaso each day exactly as your healthcare provider tells you.
- See the detailed Tyvaso Inhalation System Instructions for Use.
- Tyvaso is breathed in (inhaled) through your mouth into your lungs. Tyvaso should only be used with the Tyvaso Inhalation System.
- Tyvaso is taken in 4 treatment sessions each day during waking hours. The sessions should be at about 4 hours apart.
- At the beginning of each day, it will take about 5 minutes to prepare the Tyvaso Inhalation System. Each treatment session will take 2 to 3 minutes.
- Take your first Tyvaso treatment session in the morning and take your last treatment session before bedtime.
- Your healthcare provider may change your dose if needed.
- If you miss a dose of Tyvaso take it as soon as you remember.
- Do not let Tyvaso solution get into your eyes or onto your skin. If it does, rinse your skin or eyes right away with water.

What are the possible side effects of Tyvaso?

Tyvaso can cause serious side effects, including:

- Tyvaso may increase the risk of bleeding in people who take blood thinners (anticoagulants).
- If you have low blood pressure, Tyvaso may lower your blood pressure further.

Ask your healthcare provider if you are not sure if this applies to you.
The most common side effects of Tyvaso include:

- coughing
- headache
- nausea
- reddening of your face and neck (flushing)
- throat irritation and pain
- fainting or loss of consciousness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tyvaso. For more information, ask your healthcare provider or specialty pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Tyvaso?

- Store Tyvaso ampules in the unopened foil pack between 59°F to 86°F (15°C to 30°C) until ready to use.
- When the foil pouch is opened, Tyvaso ampules should be used within 7 days.
- Tyvaso is sensitive to light. The unopened Tyvaso ampules should be stored in the foil pouch.
- After a Tyvaso ampule is opened and put into the medicine cup in the Tyvaso Inhalation System, Tyvaso can be kept in the medicine cup for no more than 1 day (24 hours).
- Tyvaso that is left in the medicine cup at the end of the day must be thrown away.

Keep Tyvaso and all medicines out of the reach of children.

General information about the safe and effective use of Tyvaso.

Medicines are sometimes prescribed for conditions that are not mentioned in a patient information leaflet. Do not use Tyvaso for a condition for which it was not prescribed. Do not give Tyvaso to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about Tyvaso. You can ask your healthcare provider or specialty pharmacist for information about Tyvaso that is written for health professionals.

For more information, go to www.tyvaso.com or call 1-866-458-6479.

What are the ingredients in Tyvaso?

Active ingredient: treprostinil

Inactive ingredients: sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, and water for injection.

Tyvaso is a trademark of United Therapeutics Corporation.

Tyvaso is jointly marketed by United Therapeutics Corporation and Lung Rx, Inc.

Literature issued July 2009

United Therapeutics Corp.
Research Triangle Park, NC 27709 USA